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CARCINOMA OF THE CERVIX*

A CONSIDERATION OF CERTAIN PROBLEMS ASSOCIATED WITH ITS CONTROL

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ANYONE familiar with the tremendous amount of data and accumulated literature regarding cancer of the cervix must be impressed with the wisdom of serious meditation before venturing to add to the complexity of the subject. Offering an intensive study of abundant material as our justification, we tender our experience with the hope that it may be of some value in the prodigious task of unravelling the truth. Our interest, first nurtured during the twilight of the surgical era and later tempered during the tidal years of enthusiasm for radiation, remains today hopeful for the future but impressed with contemporary shortcomings. For us the years 1920 to 1930 remain a period of radiation controversy. During this time we attempted to follow the leaders in this type of work. It soon became apparent that no specific form of therapy, that no one method of administration was universally suitable. At the time, being concerned primarily with results, we failed to see any good reason for limiting therapeutic measures to one mode of attack, to any one applicator or gadget, nor to any one of the then popular technics of radium or x-ray administration. It appeared to us then, and we are even more convinced of it now, that we were dealing with individuals not alone from the standpoint of the patient but also with reference to the new growth itself. Each neoplasm presented variations as to growth propensities and extent, and only by

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complete individualization could we best understand her needs and therapeutic requirements. Only by adapting therapy to the individual could we feel that the patient was receiving maximum benefit from the remedial measures at our command. The idea of making the patient fit the treatment was therefore discarded and a program of individualiza-

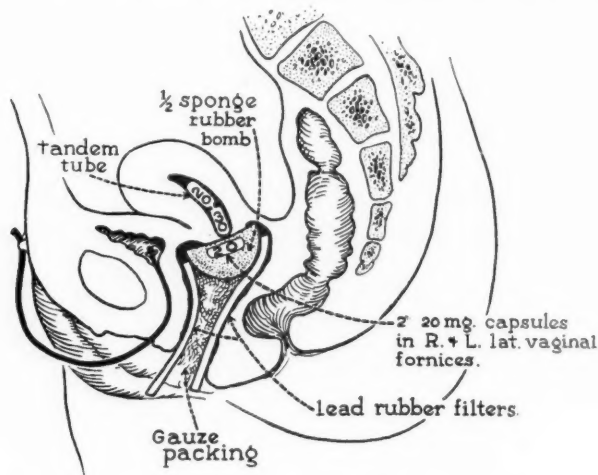


Fig. 1.—Mid-sagittal section of our radium application.

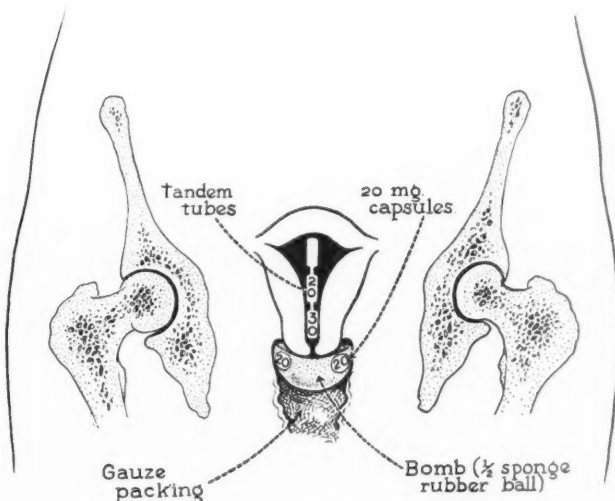


Fig. 2.—Longitudinal section.

tion inaugurated for every cancer patient admitted to the Gynecological Service at the University Hospital. It was felt that any such program, to be of real value, must include intensive study of tumor cell morphology, wide flexibility and fullest cooperation in the administration of x-ray and radium, as well as thorough evaluation of the patient's physical condition including location and extent of her tumor. To attain

this end our Gynecological Cancer Conference has been from the start a cooperative effort. Without the wholehearted interest and ceaseless toil on the part of our own staff and representatives from the Department of Roentgenology under the direction of Professor F. J. Hodges and from the Department of Pathology under the direction of Professor C. V. Weller, vigorous prosecution of our conference objectives could not have been so thoroughly carried out.

Since 1931 the conference group has met twice weekly at which time patients with cancer of the female generative tract have been carefully evaluated and individualized. From the time of its inauguration July 1, 1931, to Jan. 1, 1938, a total of 1,026 patients have been studied. This includes 47 patients treated prior to July 1, 1931. This mixed group makes our first conference year, i.e., 1931, of general statistical

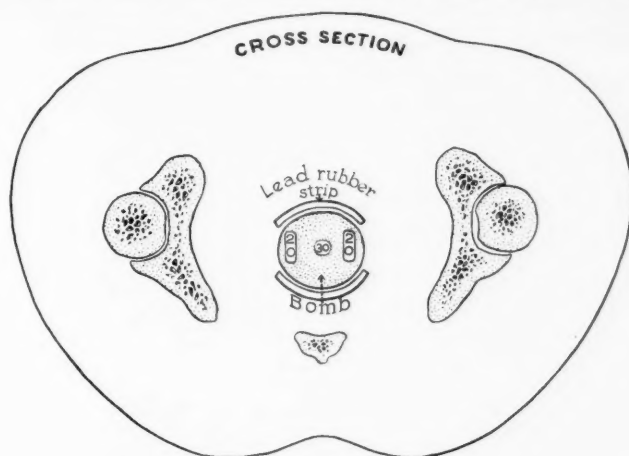


Fig. 3.—Cross section.

interest only. No attempt has been made to determine survival percentages among this group. The distribution of the lesions according to anatomic structure involved is shown in Table I. Of this total, 676 were

TABLE I. ANATOMIC DISTRIBUTION OF 1,026 CASES OF MALIGNANCY OF THE FEMALE GENERATIVE TRACT, JAN. 1, 1931, TO JAN. 1, 1938

| LOCATION OF CARCINOMA | NUMBER OF CASES | PERCENTAGE |
|-----------------------|-----------------|------------|
| Cervix | 676 | 64.91 |
| Fundus | 146 | 14.23 |
| Ovary | 94 | 9.16 |
| Vagina | 32 | 3.11 |
| Vulva | 44 | 4.29 |
| Pelvis | 10 | 1.00 |
| Clitoris | 4 | 0.40 |
| Chorioepithelioma | 5 | 0.50 |
| Fallopian tube | 1 | 0.10 |
| Bartholin gland | 1 | 0.10 |
| Sarcoma | 13 | 1.26 |
| Grand Total | 1,026 | 100.0 |

of the cervix, and it is upon data obtained from intensive study of this particular group that we base the subject matter and tables included in this report.

The source of our material is shown in Fig. 4. Practically all cases come from within the confines of the State of Michigan representing an area of 58,900 square miles. Its peculiar shape and division into two

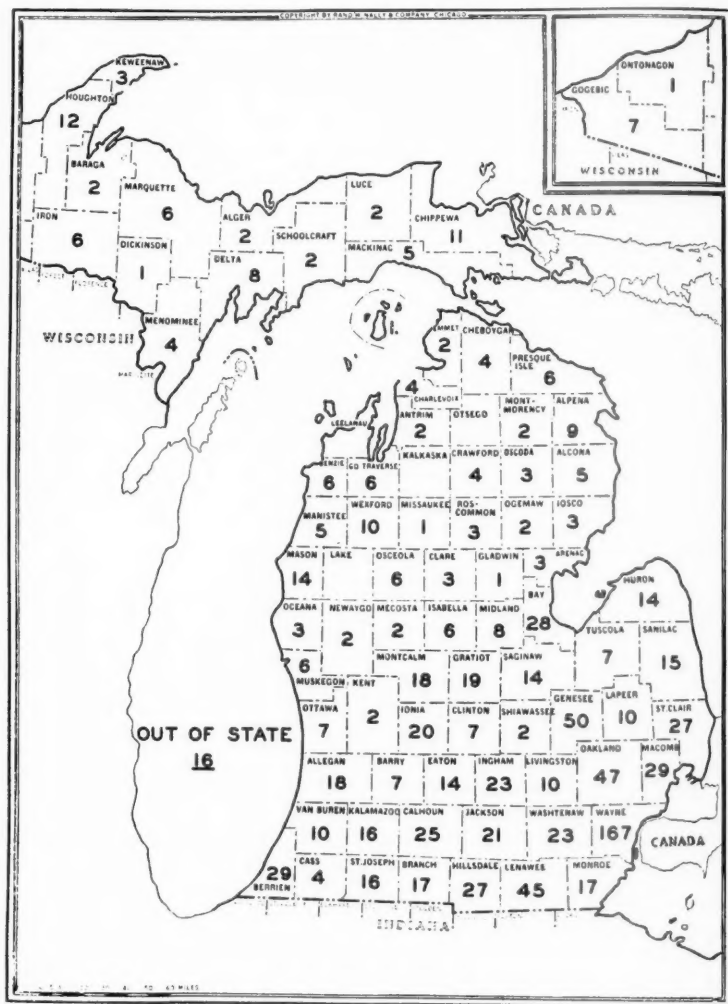


Fig. 4.—Various counties and sources of our material.

peninsulas create travel and follow-up difficulties equal to that of considerably greater area. The majority of patients come as state or county charges although many pay and private patients are also included in this study.

Table II reveals the extent of the lesions generally encountered. Fifty-seven per cent were advanced carcinomas with parametrial thick-

ening probably indicating neoplastic extension in the vast majority of cases. Twenty-seven per cent were admitted with questionable parametrial involvement, the so-called borderline group. The remaining 16 per cent was composed of Group I (4 per cent) and Group II (11 per cent) cases. Inspection of Table II will show that there occurs but little change in the clinical incidence of early and late cases from year to year. We believe this finding to be significant. It probably reflects the inefficacy of lay educational programs.

TABLE II. CARCINOMA OF THE CERVIX
CLINICAL GROUPING

| CLINICAL CLASSIFICATION | YEAR OF ADMITTANCE | | | | | | | TOTAL |
|---------------------------|--------------------|------|------|------|------|------|------|-------|
| | 1931 | 1932 | 1933 | 1934 | 1935 | 1936 | 1937 | |
| Carcinoma of cervix I | 7 | 2 | 4 | 5 | 2 | 3 | 5 | 28 |
| Carcinoma of cervix II | 11 | 7 | 10 | 11 | 10 | 15 | 12 | 76 |
| Carcinoma of cervix III | 29 | 24 | 23 | 29 | 32 | 32 | 16 | 185 |
| Carcinoma of cervix IVA | 28 | 46 | 43 | 50 | 42 | 44 | 41 | 294 |
| Carcinoma of cervix IVB | 8 | 5 | 11 | 15 | 10 | 16 | 17 | 82 |
| Carcinoma of cervix IVC | 2 | 2 | 2 | 0 | 2 | 1 | 2 | 11 |
| Total carcinoma of cervix | 85 | 86 | 93 | 110 | 98 | 111 | 93 | 676 |

Upon admittance to the clinic, a complete history is obtained, including the names and addresses of 5 relatives or friends. The latter have been particularly helpful in follow-up work which frequently presents tremendous obstacles. A complete physical examination, including biopsy and special studies as chest, bone, or intestinal x-rays, when indicated, complete the admittance data. The clinical aspects of the neoplasms are carefully noted and all data assembled to be presented when the patient is seen, examined, evaluated and individualized by the conference group. As previously stated this conference group, in addition to the gynecology staff, includes representatives from the departments of roentgenology and pathology. From one to ten or more patients, both new and return, may be considered by the conference during any one of its semi-weekly sessions. At these meetings a serious attempt is made to map a course of treatment best suited to the particular individual. Not only do we take into consideration the clinical grade and histologic type of the neoplasm but also the patient's age, general health, and other conditions peculiar to the individual which might bear significantly upon choice of therapy. The hospital owns 360 mg. of radium element split into a variety of satisfactory applicators and two 200,000 kv. deep therapy units. Consequently in choosing a course of therapy we are bound only by the practical limitations of this physical equipment and the patient's health. While treatment in general has followed accepted precepts, there has been no effort to treat every patient in exactly the same manner. Seventy-six per cent of our cases were treated with combined x-ray and radium. Ten per cent received x-ray only (advanced cases), 11 per cent were treated by other methods or combinations while 3 per cent received no treatment of any kind. Generally deep therapy x-ray preceded the radium application to the cervix and adjacent structures.

TABLE III. CARCINOMA OF CERVIX
ANALYSIS OF EXTERNAL RADIATION TREATMENT
JULY 1, 1931, TO JAN. 1, 1938

| TREATMENT | | NUMBER OF SERIES | AVERAGE NUMBER TREATMENT DAYS | NUMBER PORTS USED | INTENSITY R/MINUTE | R DOSE PER PORT PER DAY | APPROXIMATE R DOSE PER EACH PORT | TOTAL R PER SERIES |
|----------------------------------|--------------------------------|------------------|----------------------------------|----------------------|-----------------------|-------------------------------------|-------------------------------------|--------------------|
| DATE | FRE- QUENCY | | | | | | | |
| Before 1931 to July 1, 1931 | Daily | 1-5 | 3-5 | 2 | 18-30 r. | 100-200 r. to each of 2 ports | 300 to 1000 r. | 600 to 2000 r. |
| July 1, 1931, to July 1, 1936 | 2- to 4- day in- tervals | 1-4 | 7-11 | 4-6 | 30-50 r. | 150-200 r. to each of 4 ports | 1200 to 2000 r. | 8,000 r. |
| July 1, 1936, to Jan. 1, 1938 | Daily | 1 only | 15-25 | 4-6 | 50 r. | 160-200 r. to each of 2 ports | 1400 to 2200 r. | 7200 r. 8800 r. |

We suspect that almost any of the acceptable contemporary methods of radium and x-ray therapy administration will produce about the same number of five-year survivors, that today the small statistical difference in five-year results reported by various authors is due chiefly to the extent of the lesion when remedial measures are first instituted. There does, however, exist considerable difference in the morbidity from the various methods, and from this standpoint there is abundant reason to hope for improvement.

All data regarding each patient, her lesion, treatment, morbidity and follow-up are carefully recorded on code cards and then transferred to punch cards. Complete information regarding almost any phase of the disease is thus available for any year and within a relatively short time. For five and one-half years the task of follow-up was carried by our own staff. During this time every patient seen or treated by us was traced. For the past year and one-half much of this work has been shouldered by the Hospital Social Service Department under the direction of Miss Dorothy Ketcham. We are still able to report a 100 per cent follow-up on the 676 patients with cervical cancer comprising the basis for this report. A statement regarding the tremendous difficulty of maintaining a 100 per cent follow-up is certainly apropos. Yet it would be meaningless to those who have had no experience with this problem and for those who do try to maintain a high percentage follow-up no comment is needed. Every conceivable method of locating the lost cases, from contacting bureaus of vital statistics, friends, relatives, doctors, morticians, social workers and nurses to use of detectives and radio may be found necessary. At the end of each year since the conference began (1931), a summary of the work done has been prepared. This has been thoroughly digested by the conference group with the idea of making such alterations and deductions as appeared feasible. During these seven

years of intensive study we have accumulated abundant data and no little experience. While we have no intention of bombarding a few willing readers with meaningless and tedious statistics some of our observations may prove helpful and with that thought in mind we present in this first report some general data and observations.

It will be noted throughout our tables that patients are recorded as either living or dead. We do not know how many of the living still harbor an active neoplasm but from study of survival rates we would assume a majority. In recording results some authors have the habit of speaking of survivors as "alive and free from evidence of disease." We have often wondered just where these authors include their living patients *with* evidence of disease.

An analysis of yearly admittances as of Jan. 1, 1938, is shown in Table IV. It will be noted that we see approximately 100 new cervical cancers each year. It will also be noted that we have for speculative purposes appended at the bottom of Table IV deaths due to causes other than cancer.

This was not done with any intention of presenting corrected survival rates but rather with the idea of determining just how important this correction factor really is in any completely followed large group of cases. If the percentage dead from other causes is added to the survival percentage in this table the difference is readily noted. For example our uncorrected six-year (1932) survival percentage is 24.42. When we make allowance for death from other causes we have a corrected six-year survival rate of 26.74 per cent, or almost 27 per cent. Since many of the other causes of death are directly or indirectly the result of the cancer or therapy directed toward its elimination the difficulty of deciding just which deaths are to be deducted becomes and will always remain a problem. On the other hand, where adequate follow-up is possible the quoting of "absolute" or "uncorrected" results also presents certain important drawbacks. It means the inclusion of untreated advanced cases and in some clinics this is a real item (3 per cent in our series). Furthermore, if we assume that lay educational programs may with time achieve some good so that patients will report for treatment earlier in the course of the disease the correction factor is then likely to become increasingly more important. With earlier treatment and greater prolongation of life, there will come more deaths from other causes lending greater distortion to an already controversial situation.

The 19 deaths from other causes already noted in our group were distributed as shown in Table V.

In speaking of results the casual observer thinks only in terms of survivors. This is natural and logical but it should be remembered that there are other results in the form of morbidity. Indeed, we believe this to be one of the major problems of radiation therapy today. Of the many techniques available the one that can offer the lowest morbidity will in the future become the most acceptable. With existing methods of treatment and other weapons now available the advanced cervical

TABLE IV. ANALYSIS OF YEARLY ADMITTANCES AS OF JAN. 1, 1938

| CLINICAL CLASSIFICATION | YEAR OF ADMISSION | | | | | | | | | | | | | | | | |
|-------------------------------------|-------------------|----------------------|-----------------|----------------------|-----------------|----------------------|-----------------|----------------------|-----------------|----------------------|-----------------|----------------------|-----------------|----------------------|-----------------|----------------------|--|
| | 1931 | | | 1932 | | | 1933 | | | 1934 | | 1935 | | 1936 | | 1937 | |
| | NUMBER CASES | PER CENT SURVIVAL | NUMBER CASES | PER CENT SURVIVAL | NUMBER CASES | PER CENT SURVIVAL | NUMBER CASES | PER CENT SURVIVAL | NUMBER CASES | PER CENT SURVIVAL | NUMBER CASES | PER CENT SURVIVAL | NUMBER CASES | PER CENT SURVIVAL | NUMBER CASES | PER CENT SURVIVAL | |
| Carcinoma of cervix I | 7 | | 2 | 50.0 | 4 | 50.0 | 5 | 100.0 | 2 | 100.0 | 3 | 66.67 | 5 | 100.0 | | | |
| Carcinoma of cervix II | 11 | | 7 | 42.86 | 10 | 50.0 | 11 | 81.82 | 10 | 60.0 | 15 | 80.0 | 12 | 100.0 | | | |
| Carcinoma of cervix III | 29 | | 24 | 41.67 | 23 | 26.09 | 29 | 31.03 | 32 | 62.50 | 32 | 84.38 | 16 | 100.0 | | | |
| Carcinoma of cervix IVA | 28 | | 46 | 15.22 | 43 | 18.60 | 50 | 18.0 | 42 | 23.81 | 44 | 54.55 | 41 | 87.80 | | | |
| Carcinoma of cervix IVB | 8 | | 5 | 0.0 | 11 | 9.09 | 15 | 0.0 | 10 | 0.0 | 16 | 18.75 | 17 | 52.94 | | | |
| Carcinoma of cervix IVC | 2 | | 2 | 0.0 | 2 | 0.0 | 0 | 0.0 | 2 | 0.0 | 1 | 0.0 | 2 | 50.0 | | | |
| Total carcinoma of cervix | 85 | | 86 | 24.42 | 93 | 23.56 | 110 | 29.09 | 98 | 38.78 | 111 | 61.26 | 93 | 84.95 | | | |
| Dead of other causes (corrected) | 1 | | 2 | 2.32 | 2 | 2.15 | 4 | 3.63 | 3 | 3.06 | 7 | 6.30 | 0 | 0.0 | | | |

TABLE V. CARCINOMA OF CERVIX
CAUSES OF DEATH IN 19 CASES (MORTALITY CORRECTION)
JULY 1, 1931, TO JAN. 1, 1938

| CAUSE OF DEATH | NUMBER CASES |
|------------------------------|--------------|
| Terminal ileitis | 5 |
| Toxemia | 3 |
| Intestinal obstruction | 2 |
| Pelvic abscess (peritonitis) | 2 |
| Heart disease | 2 |
| Uremia | 2 |
| Second primary neoplasm | 1 |
| Mesenteric thrombosis | 1 |
| Pneumonia | 1 |
| Total | 19 |

carcinoma presents an extremely poor prognosis. In the reasonably early lesion, however, there exists some choice in treatment. In both groups the morbidity is excessive and the suffering endured by many as a result of therapy, doubtfully justified. Except for the control of symptoms many advanced cases are better untreated. While on the surface it may seem cruel and heartless to deny these patients the questionable benefit of therapy, the facts show the reverse to be true. Better symptomatic treatment and alleviation of pain for these advanced cases than added suffering through ill-advised remedial measures. Potential cures among the earlier cases are common, yet many of these patients suffer unbelievable discomfort for years as a result of therapy. Naturally this cannot always be prevented, but we believe reduction of morbidity constitutes a very important challenge to therapy in the management of cervical cancer today. While we plan to consider this phase of the problem in detail at another time we should like to point out that the skeletal system as well as the skin, urinary and alimentary tracts may reflect the effects of therapeutic attack. In 1936 fourteen cases of hip fracture among patients treated in this clinic were reported. We have now seen a total of 35 proved fractures and *many* more probable fractures. Twenty-five of the proved cases occurred in the cervical cancer group. The symptomatology, pathology, and tendency to heal have been previously described elsewhere. This complication has not been generally recognized, but to us it represents but one of the many real hazards, one of the many perhaps unavoidable but nevertheless undesirable results of contemporary treatment.

Our five- and six-year survival rates are presented in Table VII. The fact that there is nothing very remarkable about our results has a very real and special significance to us. It probably closely approaches the best that we may expect to accomplish with existing remedial measures at our command and among patients of whom 84 per cent (clinical Groups III and IV) are already advanced carcinomas. These figures more than ever impress us with the need for a different approach to the problem of lay education. Even with new and vastly improved ther-

apeutic methods, the very nature of cancer makes its complete destruction without costly damage to normal tissues an impractical likelihood except in early cases. To hope for a perfect cure is universal, but while we wait let's not overlook the good to be achieved through earlier treatment by existing methods.

TABLE VI. CARCINOMA OF CERVIX. MORBIDITY
JULY 1, 1931, TO JULY 1, 1937 (646 CASES)

| | MORBIDITY | NUMBER OF CASES | PERCENTAGE OF CASES |
|-----------|----------------------------|-----------------|---------------------|
| Immediate | None | 359 | 56 |
| | Moderate | 218 | 34 |
| | Severe | 57 | 9 |
| | Treatment mortality | 12 | 1 |
| Late | Skin (telangiectasia) | 101 | 16 |
| | Gastrointestinal | 440 | 68 |
| | Urinary | 395 | 61 |
| | Bone and joint | 134 | 21 |
| | Peripheral circulatory | 129 | 20 |
| | Severe psychoses | 17 | 3 |
| | Severe menopausal symptoms | 49 | 8 |

TABLE VII. CARCINOMA OF CERVIX. SIX- AND FIVE-YEAR SURVIVALS

| CLINICAL CLASSIFICATION | SIX-YEAR GROUP 1932 TO 1938 | | | | FIVE-YEAR GROUP 1933 TO 1938 | | | |
|---------------------------|--------------------------------|---------------|-----------------|---------------------|---------------------------------|---------------|-----------------|---------------------|
| | NUMBER CASES | NUMBER LIVING | NUMBER UNTRACED | PERCENTAGE SURVIVAL | NUMBER CASES | NUMBER LIVING | NUMBER UNTRACED | PERCENTAGE SURVIVAL |
| Carcinoma of cervix I | 2 | 1 | 0 | 50.0 | 4 | 2 | 0 | 50.0 |
| Carcinoma of cervix II | 7 | 3 | 0 | 42.86 | 10 | 3 | 0 | 50.0 |
| Carcinoma of cervix III | 24 | 10 | 0 | 41.67 | 23 | 6 | 0 | 26.09 |
| Carcinoma of cervix IVA | 46 | 7 | 0 | 15.22 | 43 | 8 | 0 | 18.60 |
| Carcinoma of cervix IVB | 5 | 0 | 0 | 0.0 | 11 | 1 | 0 | 9.09 |
| Carcinoma of cervix IVC | 2 | 0 | 0 | 0.0 | 2 | 0 | 0 | 0.0 |
| Total carcinoma of cervix | 86 | 21 | 0 | 24.42 | 93 | 22 | 0 | 23.66 |

With prolonged and intensive study of any subject there comes a time when thoughts, rather ill-defined at first, tend to crystallize. Impressions become convictions and while often unproved these convictions may nevertheless have a real place in reshaping our ideas and furthering our knowledge regarding the subject. Our study has given us a great deal of information. It has taught us much about cervical cancer and its behavior. It has also created doubt in our minds regarding certain traditional and long accepted beliefs, a few of which, because of their general nature and bearing on the whole subject of cancer control, we venture to mention at this time.

CANCER PREVENTION FROM THE STANDPOINT OF LAY EDUCATION

To deny the value of lay education with respect to cancer is to gain-say the tremendous effort put forth by countless individuals and or-

ganizations alike. The potential worthwhileness and the sincerity of purpose behind these educational efforts must be acknowledged. Yet when available data are dispassionately considered there appears to be little cause for rejoicing. The number of patients with early cervical cancers reporting for treatment continues to be low in spite of the fact that thousands of women have been made symptom conscious as a result of cancer educational movements. The fact that our own figures show practically no change of incidence in clinical groups would be of little significance, were it not that other studies reveal a similar picture. While it may be too soon to expect results from these educational drives it appears to us that there are other responsible factors. In cancer of the cervix the earliest objective evidence of trouble to the patient is irregular progressive and painless bloody spotting or other abnormal discharge. While these symptoms are generally the first noted they by no means invariably imply an early lesion. Furthermore, these symptoms are so frequently associated with other disturbances of health that their value must be considerably discounted as a means toward early diagnosis. Despite the vastly increased popular interest in cancer and the greatly improved cervical prophylaxis, the late cases still predominate. Improvement may come with time yet it seems to us that any significant change must depend on semi-annual physical examination for every woman over 35 years of age. If possible this should be achieved through education by making periodic examinations the battle cry of cancer educational programs instead of attempting to instill into a generally unscientific lay group the variable and more often unreliable symptomatology of cervical cancer. The importance of semi-annual or even yearly examination has long been recognized. It plays an important part in all health campaigns. Yet periodic examination to any real extent is probably doomed to failure at least from the standpoint of cervical cancer so long as we continue to harp on the so-called early (?) signs and symptoms.

CANCER PREVENTION FROM THE STANDPOINT OF THE PHYSICIAN

The general health benefits accruing from cervical prophylaxis cannot be doubted. The value of such prophylaxis from the standpoint of cancer prevention, however, appears to be a bird of a different feather. To question this commonly accepted cause and effect or contributing relationship will perhaps be looked upon as anything from gross misunderstanding of the subject to scientific paganism. We fully realize its delicacy and the far-reaching contingencies associated with any expression of doubt. Yet the evidence pointing to such relationship is almost entirely circumstantial. To convincingly prove this connection is obviously difficult for it has not yet been done. We do not believe the burden of proof should necessarily be borne by the supporters of this assumed relationship but would like to point out that it may be easier to disprove such affinity. Our interest in this matter goes back a considerable number of years and with intensive study of increasing ma-

terial we have become more and more impressed with the fact that in general such cause and effect relationship is largely mythical. We have previously discussed this subject in some detail and will not repeat it here, except to call attention to certain points which bear upon the subject of cancer control. Steeped in the belief that cervical cancer starts in one of the many common lesions noted in that structure the physician is likely to overlook the fact that cancer may develop in a cervix not so afflicted. Perhaps we fail to see the trees for the woods. Cervical prophylaxis as we think of it today is desirable, but there is reason to believe that by it both patient and physician are lulled into a sense of false security. That her cervix was repaired, a scar removed or an erosion treated does not mean that the danger of cancer is over. Perhaps the glare of commonly recognized lesions blinds us to other less easily recognized abnormalities (leucoplakia) of greater significance from the precancer standpoint. To close our eyes to the shortcomings of this long accepted traditional relationship is to deny the possibility of error and clog the wheels of progress. What the dentist has done for the teeth the physician can do for the body. Nothing short of semiannual or annual pelvic examination for all women of the cancer age will pave the way for successful control of cervical cancer. Should such periodic examinations become a reality, the physician's responsibility would increase tremendously, for the early diagnosis of cancer is not easy. Consequently hand in hand with such lay response must come a much wider recognition on part of the general medical profession that biopsy is still the best available method for ruling out the presence of cancer.

CLINICAL CLASSIFICATION OF CERVICAL CANCERS

While grouping of cervical cancers has no direct bearing on its control, there exists a very important indirect relationship. Most clinical classifications today are based on *interpretation* of findings rather than findings as such and are therefore unsuitable for the vast majority of physicians. In addition groupings now in use are chiefly devoted to advanced cases which at best present a poor prognosis. We are convinced that much greater emphasis should be placed on the early lesions. In other words, a premium should be placed on those lesions offering reasonable chance for cure. The advantages of so doing are obvious. That such grouping does not yet exist is revealed in the classifications still widely used. To emphasize the need for a universally acceptable classification is not new, to proffer such a grouping is not only repetition but likely to be frowned upon. We have no desire to appear presumptuous but convinced of the desirability for a more widely acceptable basis for clinical grouping we venture to revive this rather touchy subject. Two things stand out in any consideration of this sort: (1) what we should like to do; and (2) what actually can be done as determined by the limits of practicability. Any experienced examiner of cancer patients is aware of the undesirable but nevertheless very real gap which exists between these two, particularly in those borderline cases where an

attempt is made to determine the existence or absence of parametrial involvement. One need only record the independent findings of a group of experts on such cases to be impressed with their dissimilarity. This is because they attempt to interpret these borderline cases rather than because of any real difference in palpable findings. Interpretation varies much more than a mere statement of what is actually palpated. By basing clinical grouping on visible and palpable evidence rather than insisting upon interpretation a much more consistent and practical means of classification becomes possible. Impressed with the shortcomings of existing groupings we devised a composite classification based on what we took to be the desirable features of contemporary groupings so modified as to permit recording of visible or palpable findings without insistence upon interpretation of findings. Conceived in 1930 and used ever since we have repeatedly considered the advisability of returning to one of the older commonly accepted classifications. Each time the decision of the conference group has been to continue with our composite and modified grouping because of its practicability and consistency permitted among many examiners.

TABLE VIII. CLINICAL CLASSIFICATION OF CERVICAL CANCERS

| | |
|---------------------|---|
| Clinical Group I. | Any early proved lesion involving not more than one lip of the cervix or its equivalent. |
| Clinical Group II. | Any proved lesion more extensive than Group I, up to complete involvement of cervix but with <i>no parametrial thickening</i> . |
| Clinical Group III. | Group II cases with <i>questionable parametrial thickening</i> . |
| Clinical Group IV. | a. All cases with <i>definite</i> parametrial thickening or definite bladder, bowel, or vaginal involvement. b. Frozen pelvis, with or without remote metastasis. c. With fistula (for statistical and classifying purposes). |

TABLE IX. COMPARISON WITH OTHER CLINICAL CLASSIFICATIONS

| COMPOSITE (MILLER AND FOLSOME) | LEAGUE OF NATIONS | SCHMITZ | AUER |
|-----------------------------------|-------------------|---------|------|
| I | I | I | I |
| II | I | I | II |
| III | II | II | |
| IV A | III | III | III |
| IV B | IV | IV | IV |
| IV C | IV | IV | IV |

Briefly, we offer the following reasons for venturing to suggest another clinical classification for cervical cancers, thus:

1. With the intense interest in cancer and the constant drive toward earlier diagnosis, by pathologists and clinicians alike, it seems advisable that we place a premium on early cases. Their desirability warrants separate classification. Yet most groupings deal chiefly with advanced cases, which from the prognostic standpoint have little to offer.

2. Determination as to the existence or absence of parametrial thickening is not altogether a simple matter. In so-called borderline cases doubt regarding this point is exceedingly common. Why not recognize practical limitations in this respect and include this doubtful group as such (our Group III).

3. Interpretation of existing definite parametrial thickening is frequently impractical, often inaccurate and commonly inconsistent even among experienced gynecologists. Why not eliminate this confusion by simply reporting the non-existence, doubtful existence or definite presence of parametrial induration without attempting to interpret (guess) its significance (cancer? inflammatory?) except where the cause is obvious.

We do not deny imperfections in the classification used by us, but we believe it to be sound, universally applicable and can vouch for its practicability.

WHITHER NOW?

While we shall not attempt to answer this question there appears to be no harm in its asking. To evaluate the benefits of contemporary treatment requires only a proper viewing of the end results. This sounds simple enough and so it would be were the end results of treatment readily and truly available. While much may be learned from the abundant data already compiled, the end picture appears to be only too clearly concealed in a shroud. We do not wish to appear pessimistic. That radiation therapy produces growth restraint with prolongation of life is everywhere evident. When unassociated with excessive morbidity this extension of life span becomes one of the great benefits to mankind. In this respect radiation therapy takes its place with other great benefactions. Furthermore, in advanced cancers of the cervix, it holds a place of undisputed supremacy. Through its proper use countless doomed women are granted years of life. Among this group there is little reason for questioning its value. Here it reigns alone. It is to the minority, the small group of early, favorable cases, that our question applies. With the eight-, ten-, and fifteen-year follow-up reports of the pioneers in this field comes the growing suspicion that what is good for the late case is not necessarily good for the early case. The revelation that early cases treated by radiation when followed over a decade or more continue to show a progressive death rate from cancer cannot be viewed without concern. Among this early group there exists at least one other method of treatment, and we may well reconsider what surgery has to offer in this all too limited minority. Perhaps the swing from surgery to radium and x-ray has been too complete for the good of all concerned. In this connection the remarkable work being carried on by Dr. Frank Lynch at the University of California is worthy of serious contemplation. Unless prolonged follow-up study of early cases treated by means of radiation can show permanency of cure equaling that of surgery, it would appear that for these early cases, a return to surgery of adequate character is highly desirable.

DISCUSSION

DR. BROOKE M. ANSPACH.—My belief is that the operative treatment of cervical cancer will disappear. If radium is successful occasionally in the advanced cases, why not frequently in the early ones? In our own series of Class 1 cases we had 100 per cent salvage at the end of five years.

As a result of our experience with the treatment of carcinoma of the cervix at the Jefferson Hospital, we have determined upon a plan of radiation from which we hope to get a maximum result. We use a course of deep roentgen therapy and follow it immediately with an application of radium.

Even in the early stage there may be carcinoma seedlings in the cellular or the lymphatic tissue. As the deep x-ray so obviously affects the visible carcinomatous tissue in the vagina there is certainly good reason to believe that it may favorably influence any extensions and metastases in the broad ligaments. When the pelvis is flooded with the gamma rays at the outset of the treatment the outlying seedlings of the carcinoma are at least not spread any further since there is no manipulation of the parts.

The importance of filtration now is well recognized. The ideal filter is platinum 1.5 mm. equivalent to 3 mm. of lead and with this sloughing is reduced to a minimum. The fractional principle is observed by radiating from within immediately after radiating from without. As radiation of areas that have undergone fibrosis makes trouble, the carcinomatous area should be completely radiated from without and from within before this fibrosis has had time to occur. A repetition of radiation is made only when there are projecting, easily exposed, masses of carcinomatous tissue. The dose and the screening then are such as to produce no damage to the surrounding fibrotic tissues.

As Dr. Miller has said, the results in cancer clinics all over the world are more or less the same and the longer the cases are observed the less the proportion of salvage. Ward's, Heymann's, and our own ten-year salvage do not differ appreciably.

DR. EDWARD A. SCHUMANN.—In the first place, I confess to the belief that there is no treatment for carcinoma which has any definite value. I also wonder at all of us who so gracefully grasp at the five-year study salvage. Would you salvage malignant hypertension at five years, or pulmonary tuberculosis? It is my belief that most people who have cancer of the deep tissues eventually die of cancer.

On one point only is Dr. Miller's pessimism exceeded by mine, and that is the question of periodic examination of women by physicians. "There are no early symptoms of carcinoma," says Dr. Miller, "and very often no evidence." You may paint the portio with Schiller's solution and if the cancer is a little way in the cervical canal it does not show. From time to time you make a biopsy of cancer of the cervix, but you do not get the cancer. As the otolaryngologists have sold to the people the idea of tonsils as the focus of infection and the necessity of their removal I sometimes wonder if we should sell women the idea of having amputation of the cervix the moment their families are completed?

DR. WILLIAM R. NICHOLSON.—I cannot allow one statement of the writer to pass without definite criticism. This was in regard to the value of treating lesions of the cervix. A small proportion of early carcinomas of the cervix may unknowingly be cured by the skillful use of the cautery at a stage when as far as can be seen the lesion is nothing more than an erosion. Furthermore I am still willing to consider them as tending to the later development of cancer. It is a very grave mistake to say, at this period in our knowledge of cancer, that the presence of the lesion has no bearing upon the later incidence of carcinoma.

DR. CHARLES BEHNEY.—A great deal of time and energy has been expended in discussion of the merits of various techniques for the treatment of carcinoma of the cervix. Yet we all know that results are practically identical for cases with the same degree of involvement regardless of technique. On the other hand, comparatively little has been done to investigate palliative procedures. Are we

not attaching too much importance to the "five-year curability" of this disease? Should we not ask rather can this patient be returned to society a happy, comfortable woman, of use to her family, and for how long? We have at the Philadelphia General Hospital a patient who has had carcinoma of the cervix for sixteen years. During this time there have been two recurrences. Yet she has enjoyed living with her family and has served them for all of this time. Though she is undoubtedly doomed and is not a cured case, I cannot help but feel that her treatment has been brilliantly successful.

High morbidity is often the result of our zealous efforts to increase our five-year cures. At the Philadelphia General Hospital we believe that the more advanced the disease the more cautious one must be with dosage. Anspach expressed this view when he warned us to use only high voltage x-ray therapy in advanced cases.

DR. GEORGE E. PFAHLER.—An early diagnosis means more than degrees of skill or variations in the means of treatment of this disease. If we can arouse the profession at large to make frequent examinations and to pay more attention to any abnormality that is found about the cervix, a much larger percentage of early cases will be discovered.

I also am not discouraged at the lack of results from the lay education. The results have not been great because we have not yet reached the great mass of people. When we can induce all women to have a gynecologic examination twice a year or, better, four times a year, then we will surely recognize more patients in the early stage.

We are hearing a great deal today about super-voltage with 400 Kv. to 800 Kv., and we are led to expect wonderful results. I do not think we are going to change the end results very much, because such treatment is only made in advanced cases.

We know that carcinoma develops in scars in fibrous tissue, and of course, when we have treated a carcinoma of the cervix, we are leaving damaged tissue. Such damaged tissue has a lower vitality, and there is, therefore, more tendency to develop cancer in such a patient than in one who has perfectly normal tissue. After a period of 10, to 15 to 20 years, that tissue is likely to degenerate.

I agree that the palliative treatment of carcinoma of the cervix is most worth while. Some of these patients may die ultimately of carcinoma, but even so, they usually do not have the foul, sloughing carcinoma that can be diagnosed when you walk into a room. I have had the privilege of seeing patients on whom I had made a diagnosis of third stage involvement and did not estimate over 10 per cent chance of recovery, who have remained well for five or more years.

DR. CATHERINE MACFARLANE.—I wish to add further emphasis to the importance of periodic pelvic examination. With Miller, I must admit that the Campaign to Control Cancer has not accomplished the brilliant results that had been hoped for. On the other hand, I believe if Miller's statistics on this point had been carried back twenty-five years instead of five years, his conclusions would have been more valuable.

I believe certain "circumstantial evidence" has a bearing upon the significance of lacerations of the cervix in the development of cervical cancer. In a review of 1,000 white nulliparous women between 20 and 79 years of age, I found 14 cases of cancer of the cervix. In a similar series of 1,000 white parous women I found 37 cases of cancer of the cervix or almost three times as many. I should like to ask Miller how he would explain this bit of circumstantial evidence?

DR. STEPHEN E. TRACY.—Like Miller I have never believed in a standard dosage of radiation any more than I believe a patient should be made to fit some special operative technique. I was glad also to note Miller's use of the lead strips in the vagina. In our work we use 4 mm. of lead covered with 4 mm. of composition to protect the anterior and posterior vaginal walls, and we do not produce fistulas.

I differ with Miller in what he stated about the treatment of late cases. I believe that every patient should be given the benefit of irradiation, unless, of course, it is evident that the patient has but a few days to live, because once in a while a patient who seems hopeless at first visit, may be cured.

DR. B. L. CRAWFORD.—Based on the examination of biopsies from a large number of cervical lesions, I agree with the speaker that inflammations and erosions of the cervix are not necessarily precursors of carcinoma, and that true polyps of the cervix rarely, if ever, become malignant. Because of the accessibility of the cervix every suspicious lesion of this organ should be biopsied. In studying the biopsy specimen, the change in the character of the epithelium is the most important point to consider. If the epithelium is hyperplastic and undifferentiated, the lesion should be regarded with suspicion even though actual infiltration by the epithelium cannot be demonstrated.

DR. LEWIS C. SCHEFFEY.—First, it is well enough to stress the education of the laity, but we must continue to educate the doctors. It is discouraging to the teacher to bring before students case history after case history in which patients have actually gone to a physician because of their symptoms and then, either through ignorance or indifference on his part, have not been examined or given adequate treatment or advice.

Second, whether or not one is in agreement with Miller's views regarding the significance for cancer development of certain lesions of the cervix, I think that we should definitely emphasize to our students the importance of properly treating the pathologic cervix.

DR. MILLER (closing).—We teach and stress, of course, the importance of cervical prophylaxis. Correction of minor cervical pathology is important and should be continued, but on the other hand there appears to be no good reason why we should refuse to face the facts which strongly suggest that the long accepted cause and effect relationship between common cervical lesions and cervical cancer is largely mythical. I am reminded of the words of a very distinguished anthropologist who in looking at medicine said, "I am entirely serious when I suggest that it is a very myopic medical science which works backward from the morgue, rather than forward from the cradle." If we observe common cervical lesions from early development on through involution instead of beginning with the carcinoma and working back, evidence of this assumed relationship will appear far less convincing.

I believe that time and further study will reveal little difference in the incidence of cervical cancer among women who have or have not borne children.

The vast majority of our patients receive deep x-ray therapy first. This is followed by local radiation of the lesion by means of radium. I believe radiation has much to offer the advanced case but have come to doubt that it reigns supreme as a means of treatment for the very early case. That it prolongs life and retards neoplastic growth cannot be doubted. That radiation actually cures is another question. The progressive decline in the projected survival curves of patients treated with radiation is extremely significant. On the other hand early cases adequately treated by surgical means show no such progressive decline although the initial drop may have been marked. In this connection I should like to call attention to the remarkable work carried on by Frank Lynch in San Francisco. His ten- and fifteen-year follow-up studies and the long time, follow-up studies of others are likely to change our concept as to the best method of treatment for early cervical carcinomas.

THE RELATION OF THE PITUITARY GLAND TO THE MENOPAUSE

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IN CONSIDERING the etiology of the menopause we are faced with three possibilities:

1. Failure of the anterior pituitary gland.
2. Failure of the end organs (uterus, cervix, vagina and the general organism).
3. Failure of the ovaries.

1. *Failure of the Anterior Pituitary Gland.*—In view of the fact that the hypophysis is the motor for ovarian function one might assume that the ovary ceases to function because of a failure of production of the gonadotropic hormones. This is not the case. The hypophysis continues its hormone production years beyond the menopause. In fact, the anterior pituitary gland secretes a greater quantity of gonadotropic hormone after the menopause than before. Large quantities of follicle-stimulating hormone can be found in the blood and urine of castrates and in those who have undergone spontaneous menopause. Hence the stimulus from the hypophysis to the ovary is present, and in adequate quantity, but the response on the part of the ovary and of the end organs to this stimulation is absent.

2. *Failure of the End Organs.*—It might be argued that the amenorrhea of spontaneous menopause is due to a failure of response on the part of the uterus, and that the amenorrhea, per se, is an etiologic factor in the production of symptoms. We may point out that menopause symptoms may be present even though the patient is menstruating at regular intervals. Amenorrhea is therefore not essential for the development of this syndrome, and patients with secondary amenorrhea do not have menopause symptoms. The genital tract of the preadolescent is capable of response providing the stimulus is great enough. In the cases of gonorrheal vaginitis in children, it has been shown that estrogenic hormones produce a temporary vaginal epithelium of mature type. The cases of precocious sexual maturity show an early response on the part of the endometrium but not the myometrium, for the uterus remains infantile (Kurzrok, 1937). On the contrary, we do not as yet know whether the atrophic uterus of a woman in the fifties (or older) would produce a progestational endometrium when adequate quantities of estrogenic and corpus luteum hormones are supplied (Hübscher, 1933). Papanicolaou and Shorr (1936) have shown that with adequate amounts of estrogenic hormones there occurs a trans-

formation of the vaginal smear from the menopausal to that type of smear which is found in normally menstruating women during the high follicular phase of the menstrual cycle just prior to ovulation.

It is also evident that the general organism is not at fault. If sufficient follicular hormone were present, the body would utilize it. The therapeutic effect of large doses of estrogenic hormone manifests itself in a short time.

3. *Failure of the Ovaries.*—It is our belief that the menopause is due to a failure of the ovaries to react to stimuli, the gonadotropic hormones. The following questions present themselves:

a. Can the human ovary respond to gonadotropic hormones in the same manner as ovaries of other species (monkey, rat, etc.)?

b. What is the character of the response?

c. Do both ovaries in the same individual respond with equal intensity?

d. Do the ovaries of older patients respond equally as well as the ones of younger patients?

Zondek (1927) and Steinach and others (1928) have reported the experimental restoration of sexual function in old laboratory animals in which sex cycles have ceased. A reactivation of human ovaries during the menopause or shortly thereafter has been reported (Westman, 1934) but has been denied by others (Waldeyer, L., 1934).

It is important to keep in mind in considering the reaction of senile ovaries that an important difference obtains between the human and the lower laboratory animals. In all rats and mice after sex cycles have ceased, ova are still present (Waldeyer, L.) whereas, as shown some sixty-five years ago, by W. Waldeyer, ova cease to be present at or at least shortly after the menopause. To satisfy ourselves on this point, we have examined the ovaries of a number of women in and after the menopause. We have not found any ova in an extensive series of sections, although the complete serial sections of each ovary were not available. Indeed, the scarcity of ova in the latter third or fourth decade of the human reproductive period is surprising.

The reactivation of ovaries of old mice and rats might thus be expected with the administration of gonadotropic hormone. The reactivation of the senile human ovary would require the stimulation of the germinal epithelium and the new formation of ova.

MATERIAL AND METHODS

A total of 11 patients was studied. Their ages ranged from 25 to 66. They were all free from ovarian or adnexal pathology. Four patients were operated upon for the repair of retroversion and the remaining patients for uterine fibroids. The patients were injected with gonadotropic hormone, 10 with Antex-Leo, and 1 with castrate urine extract.

One gonadotropic hormone preparation which we used is derived from pregnancy mare serum, and is commercially known as Antex-Leo. This gonad-stimulating property of mare serum was first described by Cole and Hart (1930) and is the most potent gonad-stimulating substance available today. Recent results of Cole and

Hart (1934) have led them to believe that there are two gonadotropic hormones in the serum. The second hormone preparation used, namely, castrate urine extract (Gamone) was obtained from E. R. Squibb & Sons. It produces in animals follicles only when injected in moderate dosages for short periods.

The patients were injected with Antex-Leo either every other day or every day. Each dose contained 300 M.U. In the patients that were still menstruating injections were begun during or at the end of the period and continued to about the middle of the cycle. The essential operative procedure was performed as soon after the last injection as possible. There were neither local nor general reactions as a result of the injected material. The age, dosage and period of the cycle are given in Table I.

TABLE I. AGE, DOSAGE, AND STAGE OF CYCLE

| CASE | AGE | AMOUNT OF HORMONE | DAY OF CYCLE INJECTIONS | | OPERATION ON DAY OF CYCLE |
|------|-----|-------------------|-------------------------|-------|---------------------------|
| | | | BEGAN | ENDED | |
| 1 | 25 | 3,600 M.U. | 7 | 18 | 20 |
| 2 | 25 | 3,300 M.U. | 5 | 19 | 26 |
| 3 | 25 | 3,000 M.U. | 3 | 15 | 18 |
| 4 | 26 | 3,300 M.U. | 2 | 17 | 23 |
| 5 | 34 | 3,000 M.U. | 4 | 15 | 18 |
| 6 | 35 | 1,100 (Gamone) | 2 | 15 | 18 |
| 7 | 37 | 3,600 M.U. | 9 | 22 | 4 of next cycle |
| 8 | 43 | 3,600 M.U. | 2 | 14 | 16 |
| 9 | 47 | 3,300 M.U. | Menopause | ----- | ----- |
| 10 | 63 | 7,200 M.U. | | | Menopause |
| 11 | 66 | 8,800 M.U. | | | Menopause |

CASE REPORTS

CASE 1.—Aged 25. (No. 415102.) Gyn. Path. No. 9232, 9242, 9258, 9271.

Menses: 14 x 28 x 5 x moderate x 0. Last menstrual period, June 5 to 9, 1935.

Pregnancies: Term birth, living child, 1932.

Chief Complaint: Backache.

Diagnosis: Retroversion of uterus.

Antex-Leo: 3,600 M.U. from June 12 to 23, 1935.

Operation: June 25, 1935. Dilatation and curettage. Suspension of uterus. Right salpingo-oophorectomy.

Notes: Menses: Sept. 5 to 9, 1935; Oct. 5 to 9, 1935; Nov. 4 to 10, 1935.

Findings at Operation: The right ovary was enlarged, about 3 inches in length, and about 1½ to 2 inches in diameter. There were many new follicular cysts. The left ovary was enlarged, being about four-fifths the size of the right. In it, also, follicular cysts of new formation were found, but they were not as extensive as in the right.

Endometrium:

9232 Interval, fully developed, June 12, 1935.

9242 Interval, fully developed, June 17, 1935.

9258 Interval, possibly slightly secretory, June 20, 1935.

9271 Slight pro gravid, June 25, 1935.

Ovary: Many cysts, some large, 2 cm. In a surprising number the granulosa was present and healthy and the theca showed little or no hypertrophy.

In some, however, the theca interna had pronouncedly luteinized.

CASE 2.—(No. 474832.) Aged 25 years. Gyn. Path. No. 10111.

Menses: 11 x 28 x 3 - 4 x moderate x 0. Last menstrual periods, March 5, 1936 and April 2 to 6, 1936. No pregnancies.

Chief Complaint: Increase in size of abdomen.

Diagnosis: Fibromyomas of the uterus. Pelvic peritoneal adhesions.

Antex-Leo: 3,300 M.U. between April 7 and 21, 1936.

Operation: April 28, 1936. Supravaginal hysterectomy. Bilateral salpingo-oophorectomy.

Notes: Macroscopic Examination: Right ovary weighed 26 gm. and measured 7.5 by 4.5 by 2 cm. in thickest portion. Surface was dull velvety gray in color, through which numerous petechial hemorrhages could be seen. In one area on the surface an adhesion was seen which was so fibrous it resembled calcareous deposit. Distal portion of ovary was composed of a mahogany colored cyst 2 by 2 cm., surrounded by larger areas of petechial hemorrhage. On section several follicles were ruptured; these were small and filled with clear amber-colored fluid. In about central portion of ovary two small cysts were seen filled with viscid material of dull chocolate color. Mahogany-colored cyst described contained coagulated gelatinous material, homogeneous in texture, somewhat translucent and dull mahogany red in color; edges of this cyst appeared crenated.

Left ovary weighed 20 gm. (without section taken by Dr. Cockrill). It measures 7 by 4 by 2 cm. Surface was velvety gray in color; through it numerous petechial hemorrhages were seen. Surface was entirely covered by dense adhesions. The incision previously made appeared to extend only into ovarian stroma; no cystic cavity. There were, however, small cystic cavities noted filled with clear fluid of deep amber color; largest measured about 0.5 cm. in diameter.

Microscopic: Endometrium: Early progradid.

Ovary: Corpus luteum present, apparently recently formed. Had large cavity filled with blood. Theca lutein cells distinct. Only a few places having germinal epithelium. Only a *very occasional* primordial follicle. In several of the cysts the granulosa cells were absent. In some of them the theca interna showed areas of pronounced hypertrophy but hardly formed lutein cells. No normal growing follicles.

CASE 3.—(No. 357995.) Aged 25 years. G.P.N. 9546.

Menses: 11 x 4 weeks 1 week x 4 x moderate x 0, up to 5 years ago. Last menstrual periods, Aug. 2, 1935; Sept. 4, 1935; Sept. 27, 1935.

Pregnancies: i, 1930, full term; ii, 1931, full term; iii, 1931, induced abortion; iv, 1934, induced abortion.

Chief Complaint: Backache and dysmenorrhea for past 5 years.

Antex-Leo: 3,000 M.U. between September 30 and October 12.

Operation: Oct. 15, 1935.

Diagnosis: Retroversion of uterus and relaxation of pelvic floor.

Operation: Dilatation and curettage. Repair of pelvic floor. Suspension of uterus. Right salpingo-oophorectomy. Partial left oophorectomy.

Notes: May 28, returns with history of meno-metrorrhagia.

Findings at Operation: Both ovaries were found to be enlarged to the size of bantam eggs, and there were three to four cysts on each one. A very large corpus luteum cyst was resected in the left ovary.

Macroscopic Examination: Right ovary measured 4 by 3 by 3 cm. and weighed 17.5 gm. Surface was smooth and glistening and had mottled purplish white color. Ovary was very fluctuant; it appeared on the surface as though many cysts were present 0.5 to 2 cm. in diameter. On one side of ovary was a rather solid hemorrhagic appearing area. On section a number of cysts were seen filled with clear fluid.

Corpus luteum taken from left ovary measured 2.5 by 1.5 by 1 cm. and weighed 2 gm. It had a shiny glistening purplish external surface. Wall was 7 cm. thick; lumen about 0.5 cm. in diameter.

Microscopic: Ovary: A large corpus luteum filled with blood which contained an empty cyst lined by simple squamous epithelium. A large corpus luteum hemorrhagic and with much fibrin. There were many cysts in which granulosa was decreased or was absent. In the largest cyst the theca interna (?) at one side had undergone luteinization. In some others the theca interna cells were somewhat or greatly hypertrophied as if they would luteinize. Some very small (5 mm.) cysts had no granulosa. A small number of primordial follicles but no normal growing ones. Cysts, largest 15 mm. Most under 1 cm. (5-8 or 10 mm.).

Endometrium: A typical highly developed proliferative type.

CASE 4.—(No. 355152.) Aged 26 years. G.P.N. 9454.

Menses: 16 x 28 x 7 - 8 x moderate x 0. Last menstrual periods, June 17, 1935; July 20 to 28, 1935; Aug. 17 to 22, 1935.

Pregnancies: One, 1933, term birth.

Chief Complaint: Lower back pain and metrorrhagia.

Antex-Leo: 3,300 M.U. between August 19 and September 3.

Operation: Sept. 9, 1935.

Diagnosis: Retroversion of uterus, postpartal.

Operation: Dilatation and curettage. Suspension of uterus. Complete right oophorectomy.

Notes: Menses October 11 to 18. Normal in all respects.

Macroscopic Examination: Right ovary measured 5 by 2 by 4 cm. Surface was smooth and glistening and yellowish in color with large and small mottled blue areas which appeared to be multiple cysts.

Endometrium: Well-developed pregravid.

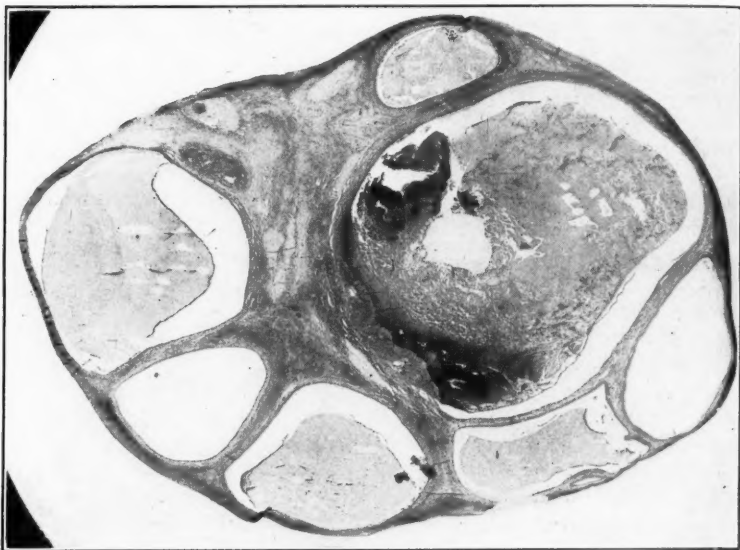


Fig. 1.—Case 3. Human ovary. G. P. N. 9546. Patient aged 25 years. Mare serum, 3,000 M. U. Large follicular cysts filled the entire ovary.

Ovaries: The other ovary was normal size. A large lutein cyst 22 by 16 mm., and there were other smaller ones which either had no granulosa or in which the granulosa was degenerating. Section B 3 (3) shows a curious follicle-like body. Some primordial follicles. Corpora albicantia present. No other lutein theca cells except in large cyst.

CASE 5.—Aged 34 years. (No. 451966.) G.P.N. 9307, 9328, 9345.

Menses: 14 x 28 x 8 x moderate x 0. Last menstrual periods, April 25, 1935; May 29, 1935; July 5 to 9, 1935.

Pregnancies: None.

Chief Complaint: Pain in back and right lower quadrant.

Antex-Leo: 3,000 M.U. between July 9 and 20.

Diagnosis: Retroversion of uterus. Salpingitis, chronic.

Operation: July 23, 1935. Dilatation and curettage. Suspension of uterus. Left salpingo-oophorectomy.

Notes: Menses, Sept. 5 to 8, 1935; Oct. 5 to 6, scant; November 5 to 8; December 9 to 10, scant; January 4 to 7; February 9 to 12; March 5 to 8.

Findings at Operation: The ovaries were not increased in size, but both appeared to be filled with small cysts.

Upon inspection of the pelvis, the uterus, tubes, and ovaries were found to be densely adherent to the posterior peritoneum.

Macroscopic Examination: Ovary measured 4 by 2 by 2 cm. Surface was smooth and glistening. It was made up of a number of small bluish cysts.

Endometrium: 9307, Typical gravid. 9328, Very hemorrhagic. Apparently only superficial tissue. Except for the large number of polymorphs in the stroma and in the gland lumina, it appeared to be typical proliferative endometrium.

Ovary: A hemorrhagic and degenerating corpus luteum from the previous cycle is present.

There were some but not many primordial follicles. A very occasional small follicle with antra, 2 seen in sections. The most noteworthy feature was the number of cysts present. All of these had a thin granulosa (2 to 4 cells thick). They varied from 3 to 7 mm. in diameter. No or but little thecal hypertrophy and no luteinization of the granulosa or theca interna.

CASE 6.—Aged 35 years. (No. 464109.) G.P.N. 9679.

Menses: 14 x 27 x 4 x moderate x 0. Last menstrual periods, Oct. 17, 1935, and Nov. 11 to 14, 1935.

Pregnancies: Questionable early abortion five years ago.

Chief Complaint: Mass in right lower quadrant. Pain in both lower quadrants. Vaginal discharge.

Operation: Nov. 29, 1935.

Castrate Urine Extract: Squibb, 1,100 R.U. given between November 12 and 26.

Diagnosis: Fibromyomas of uterus.

Operation: Dilatation and curettage. Supravaginal hysterectomy. Right salpingo-oophorectomy.

Notes: No menopause symptoms six months after the operation.

Findings at Operation: The left ovary was normal in size, and upon its anterior surface were seen five cysts, bluish-black in appearance, averaging 1½ cm. in diameter. The right ovary was enlarged to about the size of a lemon and its surface was studded with cysts resembling the others, but much larger in size. It was decided to remove this ovary.

Macroscopic Examination: Ovary measured approximately 3.5 by 2.5 by 2 cm. Surface was smooth and glistening. Part of surface was yellowish gray in color; proximal and lower two-thirds, however, have been converted into cystic mass. On external surface they appeared as small globules which were seen beneath the tissue as bluish gray in color. At outer pole was a small corpus luteum deposit showing hemorrhage on external surface. Ovary was cut with slightly less than normal resistance; cut surface was reddish gray in color and very moist and appeared quite cystic. Several small cysts were opened; they measured 1 cm. in diameter and contained bloody serous fluid. Inner surface was lined by smooth glistening purplish gray membrane; several small whitish areas were seen, one having been cut through. Here the top tissue was grayish white in color and stood up somewhat from the cut surface.

Left ovary was normal in size.

Endometrium: Interval, early gravid?

Ovary: Several cysts. In some the granulosa had disappeared and in others, it was present and had a normal appearance or showed degeneration. The theca interna cells were very slightly, if any, hypertrophied.

CASE 7.—Aged 37 years. (No. 476697.) G.P.N. 10071.

Menses: 14 x 28 x 4 x moderate x 0. Last menstrual periods, Dec. 20, 1935; Jan. 17, 1936; Feb. 14, 1936; March 2, 1936; March 22, 1936; April 13, 1936.

Pregnancies: Stillbirth, twins, fifteen years ago.

Chief Complaint: Pain in left lower quadrant.

Antex-Leo: 3,600 M.U. between April 1 and 13.

Diagnosis: Fibromyomas of uterus.

Operation: April 17, 1936. Dilatation and curettage. Supravaginal hysterectomy. Left salpingo-oophorectomy.

Findings at Operation: Patient menstruating. Right ovary small and pale without significant follicles. Left ovary was normal in size and had two small cysts.

Macroscopic Examination: Ovary measured 3 by 3 by 1.5 cm. External surface was smooth and glistening; it was covered by number filmy adhesions. It felt somewhat cystic and contained a cyst 2 cm. in diameter filled with bloody fluid. Internal surface was smooth and glistening and was purplish red in color.

Endometrium: Pro gravid probably menstruating.

Ovary: A degenerating recent corpus luteum was present. A cyst (ruptured) was present. The poorly developed lutein-like cells were probably from the theca interna. No normal primordial follicles were found in the 4 sections of the ovary available. A *very occasional* degeneration was present. No normal growing follicles. Cysts had little or no granulosa and theca interna showed hypertrophy in some.

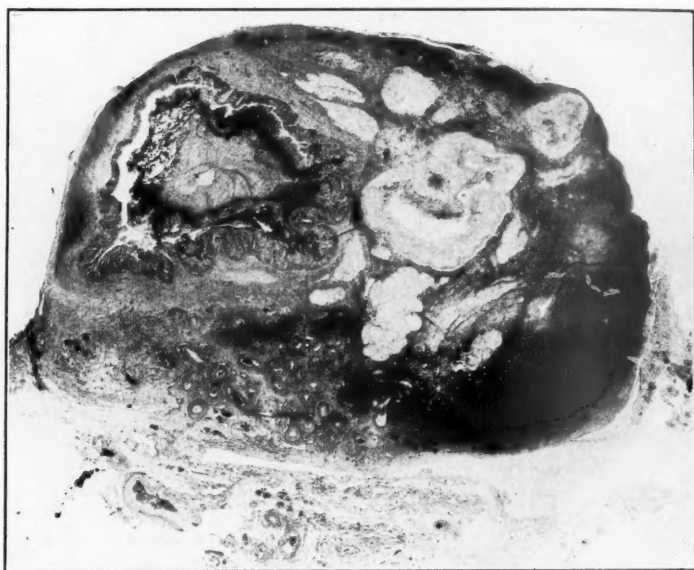


Fig. 2.—Case 8. Human ovary. G. P. N. 9298. Patient aged 43 years. Mare serum 3,600 M. U. Only one very young corpus luteum and numerous corpora albicanta.

CASE 8.—Aged 43 years. (No. 300265.) G.P.N. 9281 and 9298.

Menses: 16 x 28 x 3 x moderate x 0. Last menstrual period, June 19, 1935.

Chief Complaint: Pain in left lower quadrant.

Antex-Leo: 3,600 M.U. had been given between June 20 and July 3, 1935.

Diagnosis: Retroversion.

Operation: July 5, 1935. Supravaginal hysterectomy. Bilateral salpingo-oophorectomy. Dilatation and curettage.

Pregnancies: i, 1912, miscarriage; ii, 1913, term birth; iii, 1916, term birth; iv, 1917, miscarriage.

Progress Note: Menopause symptoms developed soon after operation and patient was seen regularly in the clinic for the relief of these symptoms.

Findings at Operation: There were numerous fine adhesions over the top of the fundus, as well as on its posterior surface. In several places, the omentum was attached to the fundus. Small areas of encysted peritoneal fluid were noted along the posterior wall of the uterus. Both tubes and ovaries were bound down to the lateral walls of the pelvis with fine adhesions. In other respects, the tubes were normal appearing. The left ovary contained a 1 cm. hemorrhagic cystic area

at one pole. Along its surface, there were several small brownish areas, grossly suggestive of endometriosis. The right ovary was normal appearing.

Macroscopic Examination: Right ovary measured 3 by 2 by 1.5 cm. It was covered by very dense adhesions, and was dark red in color with purplish discoloration. On section there appeared to be a hemorrhagic cyst 1 cm. in diameter and a smaller cyst 0.5 cm. in diameter.

Left ovary measured 3 by 1.5 by 2.5 cm. It was pale.

Endometrium: 9281, Interval (?) phase. Stroma very loose. Surface epithelium low. 9298, Interval type. Stroma dense, nuclei large. Surface epithelium high.

Ovaries: Several corpora albicantia. No growing follicles or primordial follicles. No cysts. A number of corpora albicantia. A small apparently recently formed corpus luteum which was hemorrhagic. No cysts. No growing or primordial follicles. Germinal epithelium very flat.

CASE 9.—Forty-seven years of age. Dementia precox. Irregular menstruation during past year. Jan. 20 to 30, 1936, 11 injections Antex 300 M.U. per day (total 3,300 M.U.). February 3, supravaginal hysterectomy. Bilateral salpingo-oophorectomy.

Surgeon's Report: Uterus 3 times normal size. Multiple fibroids. Right ovary, average size, no follicles observable. Left ovary, somewhat enlarged. Two cysts 1 cm. in diameter, 1 clear and 1 hemorrhagic.

Anatomy: Right ovary (Bouin). 4.03 gm. 25 by 18 by 15 mm. Some small cysts. Left ovary 6.37 gm. 30 by 25 by 15 mm. Two cysts. Each had a single layer of granulosa cells. No thecal hypertrophy. Both ovaries had corpora albicantia of varying sizes.

CASE 10.—Sixty-three years of age, colored, widow. Manic depressive psychosis. June 10 to 21, 1935, Antex 600 M.U. per day for twelve days (7,200 M.U. total).

Operation: June 24. Uterus and ovaries out.

Surgeon's Report: Ovaries totally inactive. In right ovary was a retention serous cyst.

Anatomy: Right ovary, 2.82 gm., 30 by 22 by 10 mm. Left ovary, 1.35 gm., 19 by 14 by 10 mm.

Several corpora albicantia in each ovary. No follicles or cysts except in right ovary. No granulosa or theca interna distinguishable.

CASE 11.—Sixty-six years of age. Colored. Dementia precox. April 5 to April 17, 1935, 8,800 M.U. of Antex.

Operation: Following day. Uterus and ovaries out. Uterus with fibroids. Ovaries small and unchanged by the injections.

Anatomy: Right ovary, 3.19 gm., 25 by 22 by 11 mm. Left ovary, 2.50 gm., 20 by 19 by 13 mm. No follicle or cysts visible. Several corpora albicantia present.

RESULTS

The following results were obtained:

1. There were no normal follicles.
2. The ovaries *when they reacted* showed follicle cysts. These varied in size up to 2 cm. in diameter. There were several in each ovary. The ovaries of our youngest patients were 7 to 8 cm. in diameter (immediately after removal).
3. In the three youngest patients (each 25 years of age) both ovaries showed grossly a similar reaction. In a fourth patient (26 years old) only one ovary showed a marked cystic enlargement and the other ovary appeared normal. Two other cases (patients 34 and 37 years old, respectively) showed a slight enlargement of both ovaries. They have

no growing follicles but several small cysts. The four remaining cases (patients 43, 47, 63, and 67 years old, respectively) showed no response on the part of the ovary whatsoever, even though the oldest patient received 8,800 M.U. of Antex-Leo. The reactions were greatest in the third decade of life, a slight response was present in the fourth, and a total absence of response in the fifth decade and beyond. A response may be maximal on one side and absent on the other.

4. Microscopic examination of the follicle cysts showed: (a) An absence of ova (in the sections examined to date). (b) Degenerative changes in the granulosa of varying degree. Most often there was a loss of the granulosa layer, with only one layer of cells remaining. Occasionally there appeared patchy areas of normal appearing granulosa. (c) There occurred luteinization of the theca interna and occasionally of the granulosa. Such luteinization may be associated with a pregravid endometrium. (d) One patient, Case 2, 25 years of age, showed early luteinization of the theca interna plus the granulosa layer.

5. One patient, Case 6, 35 years of age, injected with 1,100 units of castrate urine extract (Squibb) showed a cystic enlargement of one ovary to the size of a lemon, and a grossly normal ovary on the opposite side. The theca interna cells show no definite change.

CONCLUSIONS

1. The human ovary showed a loss of response to gonadotropic stimulation with age. There is a slight response in the fourth decade, and a complete absence of response in the fifth decade and beyond.

2. When the response is definite, only one ovary may show this response, while the other may show no stimulation at all. This implies the concept that one ovary can cease function before the other.

3. The injections did not induce the formation of normal follicles but resulted in multiple cysts (in the reactive ovaries) varying from 5 mm. to 2 cm. in size.

4. The menopause is due to a loss of response on the part of the ovary to gonadotropic hormones.

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THE RELATIVE VALUE OF PURE OXYGEN AND OF CARBON DIOXIDE MIXTURES IN EXPERIMENTAL RESUSCITATION*

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THE relative value of pure oxygen and of various carbon dioxide mixtures in the treatment of asphyxia neonatorum has been a subject of controversy for some years. On the one hand, Yandell Henderson¹ strongly advocates the use of carbon dioxide mixtures, recommending concentrations of this gas in oxygen which range from 7 to 20 per cent. He contends that carbon dioxide is the physiologic respiratory stimulant and believes that its stimulating effect is particularly needed in asphyxia neonatorum, because the sensitivity of the respiratory center is depressed in that condition.

Recently McGrath and Kuder² have reported observations on apneic newborn infants which were resuscitated by means of carbon dioxide mixtures, and their results lead them to concur in Henderson's views. On the other hand, Eastman,³ Kane and Kreiselman,⁴ and others, have advanced evidence which seems to indicate that pure oxygen, rather than carbon dioxide mixtures, is the ideal gas for resuscitation in asphyxia neonatorum. They base their contentions on the following considerations:

1. Actual chemical studies on the blood of truly asphyxiated infants reveal that it is already overloaded with this gas; whereas normal newborn infants have blood carbon dioxide tensions varying from 38 to 60 mm. of mercury, the blood of asphyxiated infants shows carbon dioxide tensions in excess of 65 mm., concentrations so high as to be scarcely compatible with life; to augment this excess of carbon dioxide by administering still more of the gas would seem illogical and possibly unsafe.

2. In the presence of anoxemia, which is found to a marked degree in asphyxia neonatorum, the usual respiratory stimulants, such as carbon dioxide, are known to become respiratory depressants (the "reversal" of Schmidt⁵).

3. Clinical evidence in the main indicates that pure oxygen is superior to carbon dioxide mixtures in the resuscitation of newborn infants.

In the severer forms of asphyxia neonatorum the blood is almost depleted of oxygen. Perhaps the most striking evidence of the major role played by anoxemia in asphyxia neonatorum lies in the fact that the whole clinical picture of the condition may be reduplicated both in the human being and in lower animals by reducing the blood oxygen.⁶ The sequence of events in experimental anoxemia may be described as follows: To mild degrees of anoxemia the body reacts by increased respiration and accelerated heart rate; these presumably

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are compensatory mechanisms, the first designed to bring more oxygen to the blood and the second to deliver more oxygen to the tissues. With increasing anoxemia a point is reached when these compensatory mechanisms fail to supply oxygen in amounts sufficient for cellular oxidation and then, with dramatic suddenness, "the oxygen crisis" of the physiologists, or what is termed the "reversal" by Schmidt, takes place and after this events occur rapidly. Consciousness is lost and respirations stop. Following respiratory failure there is an interval of from three to five minutes during which the heart continues to beat, but there is a marked slowing of the rate. In a typical case the slowing occurs by abrupt steps from 156 per minute before the crisis to 44 per minute in the posterisis phase. After respirations cease, sometimes a little earlier, the blood pressure rapidly declines through forty to sixty seconds. Concomitant with the drop in blood pressure the skin becomes blanched and cold, as in shock. Early in the posterisis phase of experimental anoxemia another important change occurs: the nerve muscle endings of skeletal muscle cease to function, with complete collapse of that muscular system. This results, of course, not only in flaccid extremities, but in relaxation of the sphincter ani. To recapitulate, experimental anoxemia presents the clinical picture of asphyxia neonatorum in its entirety, namely: unconsciousness, apnea, bradycardia, limp extremities, relaxed sphincter ani and the white, cold skin of shock.

The close similarity, if not identity, between asphyxia neonatorum and experimental anoxemia made it seem worth while to study the comparative value of pure oxygen and of various carbon dioxide mixtures in the resuscitation of dogs which had been rendered apneic by anoxemia. The points of particular interest for investigation were:

1. The time required to establish spontaneous breathing when various gas mixtures were used in artificial respiration.
2. The character and permanence of the re-established respiration. It has been claimed that the employment of pure oxygen in resuscitation may cause a "washing out" of carbon dioxide with resultant "acapnea." It seemed important to determine whether the re-established respirations reflected evidence of this or other abnormalities.
3. The effect of breathing 25 per cent carbon dioxide for short periods.

DESCRIPTION OF METHODS

Dogs weighing between ten and twelve pounds were anesthetized lightly with chloroform and strapped to the operating table in the usual supine position. The trachea was exposed, opened and a cannula inserted, through which nitrous oxide, oxygen, and if necessary ether were administered. Fluctuations in blood pressure were recorded in the usual manner by means of a cannula in the right femoral artery connected with a mercury manometer and slowly revolving kymograph.

Around the animal's chest and upper abdomen was placed a rubber bag which was secured in place by a loosely tied cloth casing. The bladder was inflated slightly and connected to a large tambour by means of a rubber tube, the conducting medium being air. To the rubber membrane of the tambour was affixed a pointer which recorded the respiratory excursions.

Asphyxiation was accomplished by allowing the dog to breathe 100 per cent nitrous oxide. For our purposes nitrous oxide seemed preferable to nitrogen as an asphyxiating agent for the following reasons: (1) Its anesthetic properties obviated the necessity of using other anesthetics during asphyxiation. (2) Clinical asphyxia neonatorum occurs most often in cases in which the mother has received analgesics and anesthetics; among these, concentrated mixtures of nitrous oxide not infrequently produce this condition; accordingly, the employment of this gas for asphyxiation would seem more nearly to reproduce the circumstances of asphyxia in the newborn. (3) Preliminary experiments showed that oxygen crises produced by nitrous oxide resembled closely those brought about by nitrogen, with the exception that nitrous oxide asphyxiation caused an earlier breakdown of respiration. It would seem then to offer a more severe test to any method of resuscitation used.

Following the administration of 100 per cent nitrous oxide, oxygen crises, with marked fall in blood pressure and apnea, occurred in all experiments within two to three minutes. After breathing had ceased for approximately thirty seconds, artificial respiration was instituted with a Kreiselman resuscitator,⁷ various gas mixtures being employed. In a small series of experiments, artificial respiration was withheld until sixty seconds of apnea had transpired.

At the depth of the oxygen crisis, blood samples were taken from the left femoral artery for oxygen determination. These showed oxygen which ranged between 2.3 and 4.0 volumes per cent; in severe asphyxia neonatorum the oxygen levels of the umbilical vein blood varies between 0.5 and 4.0 volumes per cent.³

RESULTS

1. *The time required to establish spontaneous breathing when various gas mixtures were used in artificial respiration:* Pure oxygen was administered in 92 experiments on 27 animals; the average time required to re-establish spontaneous breathing was forty-six seconds. Ten per cent carbon dioxide in oxygen was administered in 38 experiments on 20 animals; the average time required to re-establish breathing was fifty-two seconds. Twenty-five per cent carbon dioxide in oxygen was employed in 23 experiments on 15 animals and the average time necessary for resuscitation was forty-nine seconds. Thus, from the standpoint of time, the results obtained with pure oxygen and with carbon dioxide mixtures were almost identical when the period of apnea was thirty seconds. The results of two typical experiments, in one of which pure oxygen was used as the resuscitating gas and in the other 10 per cent carbon dioxide, are shown in Figs. 1 and 2.

As noted above, a small series of 8 animals were subjected to asphyxial apnea for sixty seconds. In four of these animals resuscitation was first attempted with 10 per cent carbon dioxide. When this gas alone was used, success was met in but one experiment out of the four and this after two minutes. In two instances, after three minutes' insufflation with 10 per cent carbon dioxide had failed to initiate spontaneous breathing, pure oxygen was administered and respiration began within ninety seconds. In the fourth experiment, cardiac action ceased after two minutes of attempted resuscitation with 10 per cent carbon dioxide. In the remaining four animals, resuscitation was attempted with 100 per cent oxygen. Spontaneous respiration was established in 3 cases after one minute, ninety-five seconds, and two minutes, respectively. In the fourth animal the administration of pure oxygen for three minutes was unsuccessful; this was followed by insufflation with 10 per cent carbon dioxide, but the animal died two minutes later. Individual variations in the ability of animals to withstand asphyxiation make conclusions in this group difficult. The observations suggest, however, that pure oxygen is preferable to 10 per cent carbon dioxide as a resuscitating agent when the asphyxiation is profound.

2. *The character and permanence of the re-established respiration:* When pure oxygen was used as the resuscitating gas, the re-established respiration was regular and apparently normal in character, as may be seen in Fig. 1. It was sustained indefinitely and in no instance was further resort to artificial respiration necessary. The blood and pulse pressures returned quickly to their normal levels. These animals which had been resuscitated with pure oxygen withstood subsequent

asphyxiation and resuscitation well, and it was usually possible to repeat the procedure six or more times. On the other hand, when carbon dioxide mixtures were employed in resuscitation, it was frequently observed that the re-established respiration was of an irregular and convulsive type. Not uncommonly it became more and more shallow, terminating in a recurrence of the apnea. This gasping, irregular type of breathing, which frequently follows experimental resuscitation with carbon

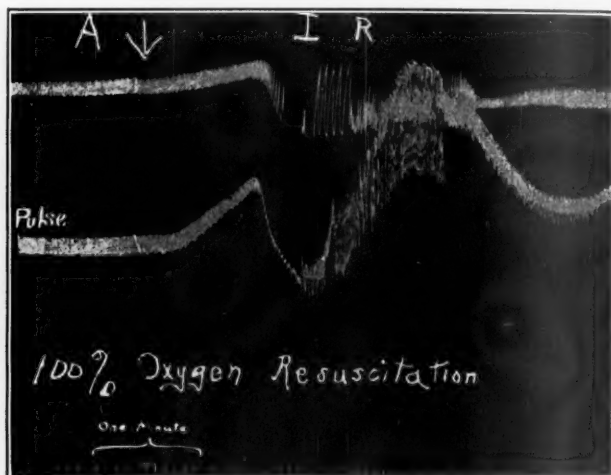


Fig. 1.—Showing the oxygen crisis of experimental anoxemia followed by resuscitation with 100 per cent oxygen. Asphyxiation is started at A. Within two minutes the blood pressure, together with the pulse pressure, falls (lower tracing), while respiration ceases (upper tracing). At I artificial respiration is begun, spontaneous breathing being initiated at R. The restored respiration is normal in rate and rhythm and remains permanently established. The blood and pulse pressures also return to normal.

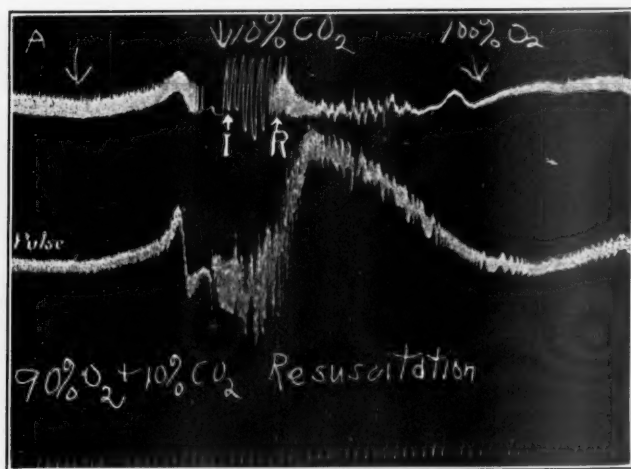


Fig. 2.—Showing the oxygen crisis of experimental anoxemia followed by resuscitation with 10 per cent carbon dioxide in oxygen. Asphyxiation is started at A. Within two minutes the blood pressure, together with the pulse pressure, falls (lower tracing), while respiration ceases (upper tracing). At I artificial respiration is begun, spontaneous breathing being initiated at R. The restored respiration is irregular and convulsive in type and soon becomes shallow, while the pulse pressure shows irregularities. Improvement follows the administration of 100 per cent oxygen.

dioxide mixtures, is shown in Figs. 2 and 3. In our experience it persisted for one or two minutes after the onset of spontaneous breathing (R) and then changed into a regular but shallow type of breathing. In both of these experiments it became so very shallow that administration of 100 per cent oxygen was deemed necessary to save the animal; apparent improvement in the respirations then occurred. Fol-

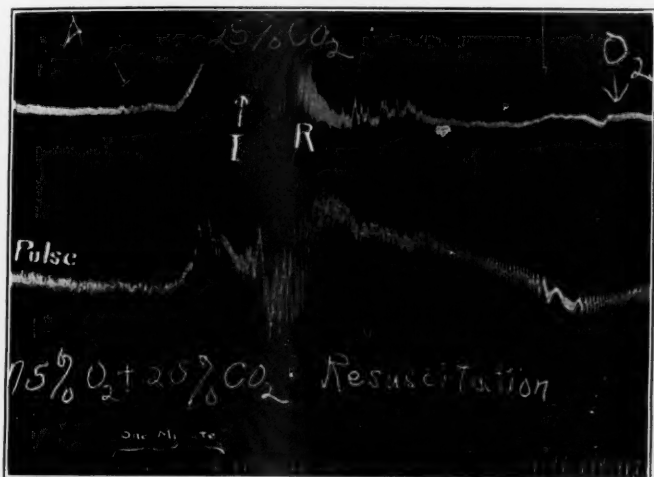


Fig. 3.—Showing the oxygen crisis of experimental anoxemia followed by resuscitation with 25 per cent carbon dioxide in oxygen. Results similar to those shown in Fig. 2. Symbols the same as in Figs. 1 and 2.

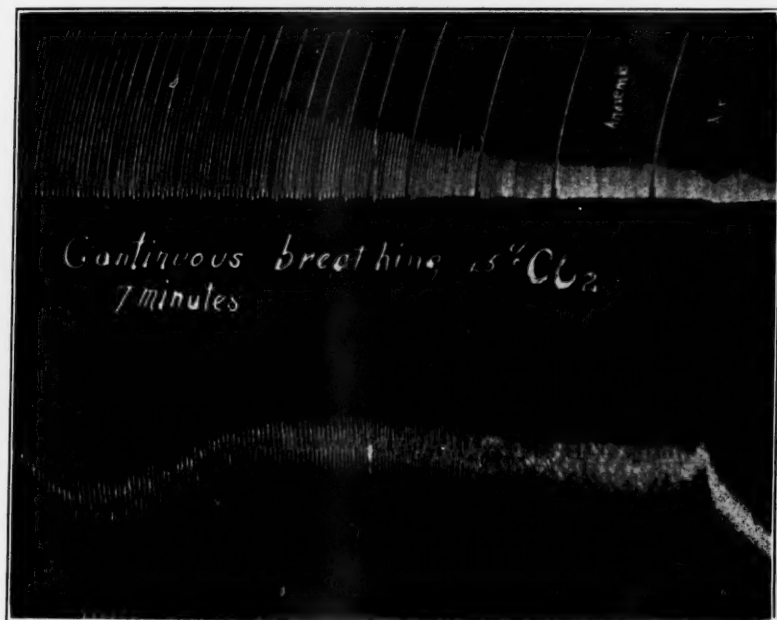


Fig. 4.—Showing the effect of breathing 25 per cent carbon dioxide in oxygen for seven minutes. Marked hyperpnea ensues followed by gasping respiration which soon becomes very shallow. In this experiment air was administered at O, but breathing remained shallow and death occurred six minutes later.

lowing resuscitation by carbon dioxide, the pulse pressures failed to return to their previous configuration and showed decided irregularities for five minutes or more. These animals, moreover, withstood subsequent asphyxiation and resuscitation poorly, and it was rarely possible to repeat the procedure more than three times without losing the animal. Our observations, therefore, afford no foundation for the contention that resuscitation by pure oxygen causes a "washing out" of carbon dioxide with resultant apnea. In our ninety-two experiments with pure oxygen nothing suggestive of such a phenomenon was observed. On the contrary, as we have indicated, it was only when carbon dioxide mixtures were used for resuscitation that abnormal types of respiration ensued.

3. *The effect of breathing 25 per cent carbon dioxide for short periods:* Since mixtures of 25 per cent carbon dioxide, or even more, have been recommended for the treatment of asphyxia neonatorum^{1, 13} and since it is occasionally necessary to employ artificial respiration in these cases for long periods, it seemed desirable to observe the effect of this gas when administered to animals in high concentration over certain intervals of time. Six animals were allowed to breathe a gas mixture containing 25 per cent carbon dioxide and 75 per cent oxygen for periods varying between seven and fifteen minutes. As is shown in Fig. 4 marked stimulation of respiration immediately followed. Soon, however, gasping respiration occurred and the animal became cyanotic, while the blood pressure fell. In the experiment illustrated the carbon dioxide mixture was withdrawn after seven minutes and air substituted; nevertheless, the respiration became more and more shallow and death followed shortly. Two other animals died after breathing 25 per cent carbon dioxide in oxygen for fifteen minutes. Similar experiments were carried out more than fifty years ago by Friedländer and Herter⁸ with comparable results.

DISCUSSION

It is well known that carbon dioxide produces toxic effects even when breathed in weak concentrations. Continuous breathing of an atmosphere containing 1 per cent carbon dioxide will incapacitate men for work and 6 per cent will usually cause subjective symptoms of malaise, headache, nausea, and even unconsciousness. Brown⁹ has found that the majority of men working in submarines were completely incapacitated when 6 per cent concentrations of carbon dioxide were reached. Noticeable hyperpnea occurs when the inspired air contains as little as 2 per cent and as the concentration reaches 10 to 15 per cent distinct dyspnea results; but beyond this point further concentration of carbon dioxide, instead of augmenting respiration, decreases it. When concentrations of 40 to 50 per cent are reached death occurs at once, without convulsions, but with the appearance rather of a fatal narcosis. In Howell's¹⁰ opinion it is probable that carbon dioxide in these concentrations exercises a direct toxic action on the nerve cells. Recently Becker¹¹ has shown that the toxic effect of carbon dioxide is not dependent upon its acid character but upon other properties: a specific lethal action on protoplasm coupled with an ability to penetrate cell boundaries with extreme rapidity. In the presence of anoxemia the harmful effects of carbon dioxide become accentuated. Schmidt⁵ has shown that when the oxygen content of the blood has been lowered sufficiently to bring about an oxygen crisis, carbon dioxide becomes a respiratory depressant. Recent experimental studies by Gellhorn¹² indicate that under conditions of oxygen deficiency 3 per cent carbon dioxide in the inhaled air increased the fall in body temperature over that observed in oxygen

deficiency alone, an effect that is particularly undesirable in asphyxia, because the body temperature has already been lowered by vascular collapse.

In the present series of experiments this toxic action of carbon dioxide on protoplasm appears to have manifested itself in several ways: first, by the convulsive, unstable character of the respiration following resuscitation by this gas; second, by the inability of animals which had been resuscitated by carbon dioxide mixtures to withstand repeated asphyxiation; and finally by the lethal effect of this gas when inspired in a concentration of 25 per cent for a long period. As resuscitating agents, these carbon dioxide mixtures showed no points of superiority over pure oxygen. In our hands, then, pure oxygen appeared to be preferable to carbon dioxide as a resuscitating agent in experimental anoxemia. While this conclusion is not necessarily applicable to asphyxia neonatorum, it is in keeping with the view that in that condition also pure oxygen is the preferable gas.

SUMMARY

1. The apnea of experimental anoxemia in animals reduplicates exactly the clinical picture, as well as the blood oxygen levels, of asphyxia neonatorum.

2. When animals are asphyxiated to the stage of apnea, resuscitation is accomplished just as quickly by insufflation with pure oxygen as it is with carbon dioxide mixtures; in the presence of profound asphyxia, pure oxygen is more efficacious than carbon dioxide.

3. Following resuscitation with pure oxygen the restored respiration remains normal in rate, amplitude, and general character, but following resuscitation with carbon dioxide mixtures the respiration tends to be convulsive and irregular; it frequently becomes shallow so that further artificial respiration is needed.

4. If animals are allowed to breathe 25 per cent carbon dioxide in oxygen for 7 to 15 minutes, grave toxic effects are produced which often result in death.

5. In experimental anoxemia pure oxygen is superior to carbon dioxide as a resuscitating agent, a circumstance which is in keeping with the view that pure oxygen is likewise preferable in the treatment of asphyxia neonatorum.

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DISCUSSION

DR. JOSEPH KREISELMAN.—During the past ten years many articles have been written on the subject of asphyxia neonatorum, but as far as I know all articles except those of Drs. Eastman, Kane, and myself have recommended carbon dioxide. Yet there is no experimental evidence to prove that carbon dioxide is the agent to use. We do know of recent work, however, contraindicating carbon dioxide in all other forms of asphyxia. This is also true with anesthesia, particularly in the use of such depressant anesthetics as cyclopropane. Respiration ceases when we use carbon dioxide. This has been shown also in New York University where experiments are being done with the barbiturates.

DR. H. P. RAMSEY.—The experimental work offered here has been conducted entirely on animals that have already been breathing and have their respiratory mechanisms functioning, while with the infants who have not breathed another situation is present. Has this difference no bearing on the discussion?

DR. JAMES F. DAVIDSON.—One thing that we are up against in all these problems is the preliminary medication given by the obstetrician. Morphine, for example, is a depressant not only to the mother, but to the child. If the latter is born within an hour or two after the administration of morphine sulphate there is a special problem in getting the infant to breathe.

DR. E. KIRBY SMITH.—There are many other factors in so-called asphyxia neonatorum besides the lack of oxygen. Many things preceding the birth of the infant may depress the respiratory center. Not only the opiates, but perhaps a certain amount of shock may have some bearing upon it.

DR. SOLLIE KATZMAN.—Henderson certainly advocates CO_2 , but not to the extent of 25 per cent of carbon dioxide and 75 per cent of oxygen. A 25 per cent mixture of CO_2 is not a resuscitant but an anesthetic and will put the patient to sleep. I am surprised that Dr. Eastman got any of his infants to breathe at all with a 25 per cent mixture.

Dr. Ebersole of the Lahey Clinic in Boston has introduced the use of helium in a mixture of 80 per cent helium and 20 per cent of oxygen. It is used not only in resuscitating infants but also during anesthesia where there is an obstruction. The helium is used because of its lighter density in getting to the lungs and ease of aeration. Helium may be a point to remember in future experiments.

DR. S. M. DODEK.—Some six years ago, working with the Departments of Pharmacology and Obstetrics at Western Reserve, we were using Dr. Kreiselman's apparatus with pure oxygen to resuscitate the newborn, and we had very excellent results. We subsequently switched to the use of pure compressed air for resuscitation of the newborn infant, and we found that every depressed newborn who had no birth injury or atelectasis could be resuscitated within a period of twenty minutes with pure air.

DR. HOWARD KANE.—About ten years ago when the Kreiselman apparatus was being developed, a question arose as to what was the better gas to use. It seemed to us that the babies all had the appearance of having too much CO_2 , so we took samples of blood from 100 cords and had them examined quantitatively for CO_2 and oxygen. We divided the babies into three groups: First, those that were born crying; second, those that were born with delayed respiration; third, those that had to be resuscitated. The crying babies had a small amount and the babies needing resuscitation had a large amount of CO_2 , which seemed to us to prove that CO_2 was not needed.

DR. NICHOLSON J. EASTMAN.—With regard to Dr. Ramsey's comment, you remember I closed my remarks by saying that it is hazardous to carry over from animal experimentation, particularly in asphyxia neonatorum, any conclusions. I said particularly asphyxia neonatorum because there we have an infant who has not breathed air before. Much as we should like to carry out such experiments in newborn animals, technical difficulties have made that impossible.

In studies on the oxygen content of newborn babies' blood, the constant finding in true asphyxia is low oxygen and by definition the constant finding in experimental anoxemia is low oxygen. Other similarities seemed to make it justifiable to carry out this study, and with the reservations that I have mentioned to apply it to asphyxia neonatorum.

Dr. Katzman misunderstood me. We did not administer 25 per cent carbon dioxide to infants, but only to these dogs who showed the usual anesthetic effects. In the bibliography is a reference to a article published by Dr. Yandell Henderson in the *Journal of the American Medical Association* I believe in 1931, in which he states that in ordinary cases of asphyxia neonatorum 7 per cent carbon dioxide is used, but that in severe examples of this condition 25 per cent may be necessary. I took the liberty of using Yandell Henderson's recommendation of 25 per cent in severe cases of this condition.

THE PLACENTAL TRANSMISSION OF NEOARSPHENAMINE IN RELATION TO THE STAGE OF PREGNANCY

WITH SPECIAL REFERENCE TO THE PRENATAL TREATMENT OF SYPHILIS

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THE present investigation is an attempt to measure one aspect of placental function, namely the capacity of the placenta to transmit substances from the mother to the fetus. A single injection of neoarsphenamine was given to rabbits at various stages of pregnancy; after a constant interval of time, quantitative determinations were made of the arsenic content of the fetuses and of the placentas. It was thus possible to determine the rate of arsenic transmission by the placenta at various stages of pregnancy.

A second object of the present experiments was to elucidate the mechanism of the antisyphilitic effect upon the fetus of arsenicals administered during pregnancy. It has been a matter of uncertainty whether there is transmitted to the fetus a sufficient concentration of therapeutically active arsenic to influence infection, or whether the placental arsenic is alone effective in prenatal treatment.

METHODS AND MATERIALS

In a typical experiment 2 c.c. of a freshly prepared solution of neoarsphenamine (Merek) were injected into the ear vein of a rabbit, the dilution being made so that the amount injected contained 0.020 gm. of the arsenical per kilogram of body weight. This represents the therapeutic dosage for the rabbit (Kolle; Kolmer, 1926), and although somewhat greater than the corresponding dosage for the human being, is still well within the limits of safety, the therapeutic index for the rabbit being 1:10 (Kolle). In two experiments this dosage was doubled, 0.040 gm. per kilogram of body weight being injected, but in no instance was the injected drug observed to exert any untoward effect upon the normal course of pregnancy, labor, nor any deleterious effect upon the fetuses. All ampoules of neoarsphenamine were from the same batch of manufacture; our analysis showed the arsenic content to be 20 per cent.

Following the administration of the neoarsphenamine, the rabbit was kept at rest for a definite period of time, after which it was rapidly killed by the injection

of 5 to 10 c.c. of air into the ear vein. The abdomen was quickly opened and the uterus excised. After opening the uterus, each fetus was removed with its placenta, which was readily separated from the uterine wall. The umbilical cord was severed close to the body of the fetus and the latter weighed with one or more of its litter mates, after the membranes had been carefully stripped from its body. Only those fetuses which showed active movements after rupture of the membranes and which showed no developmental defects were taken for analysis. In all cases at least two fetuses were taken, one being selected from each uterine horn; at early stages when the fetuses were small, four were selected and combined for analysis. The fetuses, after being carefully washed in a stream of distilled water to remove any adhering debris or amniotic fluid, were finely minced into a large Kjeldahl flask by means of heavy scissors.

Two placentas were also taken for analysis from each of twelve litters. The maternal and fetal portions were separately analyzed in seven of the experiments. Separation of the maternal from the fetal portion was easily and effectually accomplished by gentle traction with forceps. No attempt was made to wash the placentas of the gross blood which they invariably contained. After being weighed on watch crystals, the placentas were similarly minced into Kjeldahl flasks.

As no satisfactory method was available for the estimation of minute quantities of the various decomposition products of the arsphenamines, it was necessary to confine the analyses to the estimation of total arsenic.

The tissues were ashed immediately in a mixture of sulfuric and nitric acids and then analyzed by a modification of the Gutzeit method, which depends upon the liberation of arsine (AsH_3), producing a brown stain upon a paper strip previously sensitized with mercuric bromide (Association of Official Agricultural Chemists, 1931). Estimation of arsenic is made by comparison of the intensity and length of this color stain with standard stains simultaneously prepared from a stock solution of arsenic trioxide (As_2O_3). Accordingly, the readings are expressed in terms of arsenic trioxide.

Since the chemical analysis in each experiment was done jointly on two or more fetuses from the litter, the results represent the average arsenic content as calculated for a single fetus. Similar calculations were made for the placentas.

Duplicate and control determinations showed the analytical methods to be reliable as well as extremely sensitive, serving to detect as little as one-half micromilligram (thousandth of a milligram) of arsenic trioxide. With quantities exceeding 2 micromilligrams, readings were made to the nearest micromilligram. Smaller quantities were estimated to the nearest half-micromilligram. All reagents used in the analytical procedures were arsenic-free, blank controls being run with each set of determinations. Repeated tissue controls upon newborn rabbits were uniformly negative, never showing more than a faint trace of arsenic, too small for estimation. As a further check on the method, it was shown that the arsenic which was recovered by ashing a newborn rabbit a few minutes after an injection of neoarsphenamine into it, agreed remarkably closely with the arsenic content of the injected drug.

The observations are based upon analyses of 44 fetuses and 24 placentas which were obtained from the litters of 24 healthy, multiparous rabbits at various stages of pregnancy from nineteen to thirty-five days. Accurate estimation of the stage of pregnancy was assured, since the animals were isolated in separate cages and mated in the laboratory.

The average period of gestation in the rabbit is normally thirty-two days. In some of the experiments, however, it was desired to prolong pregnancy, inhibition of labor being accomplished by a single intravenous injection of antuitrin-S (Parke, Davis & Co), 1 c.c., twenty-five days after insemination. It is understood that all pregnancies of more than thirty-two days' duration were prolonged in this manner (Snyder, 1934).

The rabbit was selected as a favorable animal for study, because of the structural similarity of its placenta to that of the human being, both being of the hemochorial type (Grosser, 1927).

OBSERVATIONS

Fetus.—In a series of 24 fetuses obtained from 12 litters which were sacrificed at various stages of pregnancy, there were striking differences in the quantities of arsenic which were recovered from the fetuses upon examination one hour following injection. The arsenic content per fetus varied from none to 8 micromilligrams. When the stage of pregnancy was taken into consideration, it was evident that a definite correlation existed between the age of the fetus and its arsenic content. At twenty-five days no arsenic could be detected in the fetus. At twenty-seven days a small amount, estimated to be $\frac{1}{4}$ micromilligram, was found. From the beginning of the period of viability, that is, twenty-eight days, increasingly larger amounts of arsenic were found in the fetus as pregnancy progressed, the greatest amount in the series, 8 micromilligrams, being recovered at thirty-four days, or two days past term.

When the increase in weight of the fetus was taken into account, it was found that the arsenic content per unit weight of fetus also increased as pregnancy progressed, the curve being roughly parallel to that representing the total arsenic content (Fig. 1).

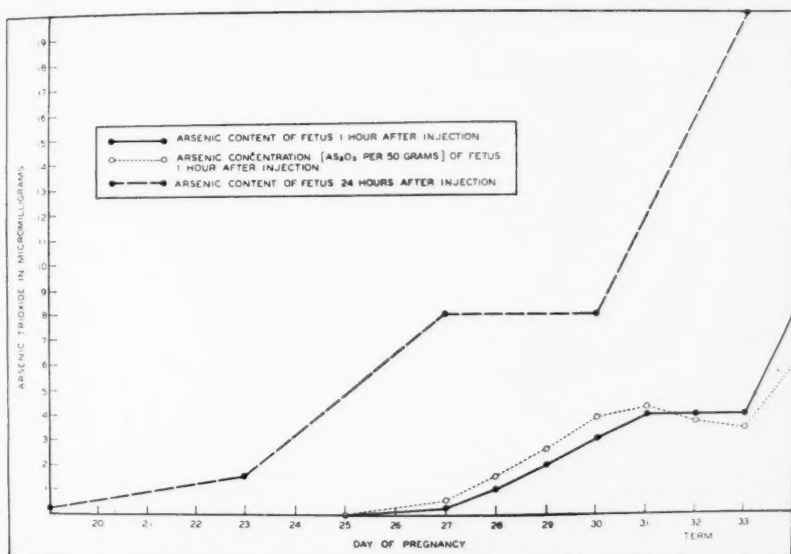


Chart 1.—The rate of transmission of neoarsphenamine from mother to fetus increases as pregnancy progresses. Each dot represents the result of analysis of at least one litter; at the twenty-eight- and the twenty-nine-day stages in the one-hour series, the results are based upon agreement of analyses of two and three litters, respectively. The abscissa denotes the stage of pregnancy at the time of injection.

In a second series of 14 fetuses obtained from 5 litters in which a longer period of time, namely, twenty-four hours, elapsed following injection, it was found likewise that the amount of arsenic in the fetus increased as term was approached. Arsenic was detected at an earlier stage of pregnancy than in the one-hour series, $\frac{1}{4}$ micromilligram being recovered in a fetus at nineteen days. At the opposite extreme, namely, in postmature fetuses examined at thirty-four days, the arsenic content of a single fetus reached the maximum of the series, 20 micromilligrams, as compared with a maximum of 8 micromilligrams recovered one hour after injection at the same stage of pregnancy. At a given stage of pregnancy a larger quantity of arsenic was in the fetus twenty-four hours following injection than after one hour. The arsenic content per unit weight of fetus also increased as pregnancy progressed, the curve of arsenic concentrations being roughly parallel to that representing the total arsenic content after twenty-four hours.

Two litters were sacrificed for analysis seventy-two hours following injection. The maternal animals were injected at nineteen- and twenty-eight-day stages, respectively, with the same dosage of neoarsphenamine, 0.020 gm. per kilogram of body weight, and determinations were made on 6 fetuses. The nineteen-day fetus was found to contain a trace of arsenic, while in striking contrast to this, the twenty-eight-day fetus contained 14 micromilligrams.

The effect of doubling the dosage of neoarsphenamine, administering 0.040 gm. instead of 0.020 gm. per kilogram of body weight, was observed in four fetuses obtained from two litters sacrificed one hour after injection at twenty-nine days. There was recovered in one litter 2 micromilligrams of arsenic per fetus, and in the other, 3 micromilligrams. In the three rabbits injected with the standard dosage of 0.020 gm. per kilogram at this stage of pregnancy, each of the fetuses contained 2 micromilligrams of arsenic after the same interval following injection. It is thus evident that doubling the amount of the drug which the mother received did not produce a proportionate increase in the placental transmission of it.

Placenta.—The placenta consistently contained a total amount and concentration of arsenic which were considerably greater than those in the fetus. Examination was made in all cases one hour following the injection of the standard dosage of neoarsphenamine, 0.020 gm. per kilogram of maternal body weight. In 24 placentas obtained from 12 litters which included stages from the twenty-seventh to the thirty-fifth day of pregnancy, the arsenic content averaged 71 micromilligrams. The maximum arsenic content of a placenta was 100 micromilligrams; the minimum was 49 micromilligrams. The concentration of arsenic averaged 14 micromilligrams per gram of placenta, ranging between a maximum of 18 and a minimum of 8 micromilligrams per gram.

Separate determinations of the arsenic content of the fetal and maternal portions of the placenta showed that the total amount and concentration of the arsenical were without exception greater in the fetal than in the maternal portion (Table I).

TABLE I. ARSENIC CONTENT OF PLACENTA ONE HOUR AFTER INJECTION OF NEOARSPHENAMINE AT VARIOUS STAGES BETWEEN THE 27TH AND 34TH DAYS OF PREGNANCY

| ARSENIC TRIOXIDE IN MICROMILLIGRAMS | | | | | | |
|-------------------------------------|---------|---------|------------------------------|-------------------------------------|---------|------------------------------|
| | MAXIMUM | MINIMUM | AVERAGE (SERIES OF 14) | CONCENTRATION (As_2O_3 PER GRAM) | | |
| | | | | MAXIMUM | MINIMUM | AVERAGE (SERIES OF 14) |
| Total placenta | 84 | 49 | 65 | 17 | 8 | 13 |
| Fetal portion | 75 | 40 | 56 | 20 | 9 | 15 |
| Maternal portion | 12 | 7 | 9 | 11 | 4 | 7 |

In 14 placentas obtained from 7 litters which represented stages of pregnancy from the twenty-seventh to the thirty-fourth day, the average arsenic content was 56 micromilligrams in the fetal portion and 9 micromilligrams in the maternal portion (Table I). The average concentration of arsenic was twice as great in the fetal portion as that in the maternal portion.

The fetal portion, which averaged in this series 73 per cent of the total placental weight, was found to contain 86 per cent of the placental arsenic. The maternal part, on the other hand, representing 27 per cent of the placental mass, averaged only 14 per cent of the total arsenic content.

No correlation could be established between the stage of pregnancy and the arsenic content of the placenta.

DISCUSSION

The foregoing observations represent a quantitative determination of the activity of the placenta at various stages of pregnancy, using as a

measure of placental function the amount of arsenic which is found in the fetus after the injection of the mother with neoarsphenamine. Under conditions standardized with respect to dosage and time interval following administration of the arsenical, there is revealed a progressive increase in the rate of placental transmission of arsenic from mother to fetus as pregnancy approaches termination. The amount of arsenic which passes the placenta within a definite time interval is a function of the stage of pregnancy, being roughly proportional to the age of the fetus.

The present findings are supported by a previous investigation in which the stage of pregnancy was found to be an important factor in the rate of transmission of a substance across the placenta in the opposite direction, that is, from fetus to mother (Lell, Liber and Snyder, 1932). Following the injection of fetuses in the uterus with phenolsulphonphthalein, the rate of excretion of the dye from fetus to mother was found to vary with the stage of pregnancy, but in an inverse direction, the output of the dye progressively decreasing as term was approached. In this investigation, as well as in the present experiments, the rate of placental transmission was governed by a gradient which was related to the stage of pregnancy.

It is clear, therefore, that any investigation of the placental transmission of a substance, be it from mother to fetus or vice versa, must take into consideration the stage of pregnancy as a factor of the first importance. Neglect of this factor and lack of sensitivity of analytical methods may account for the failure of previous investigations (Meyer, 1915; Underhill and Amatruda, 1923) to reveal more than a trace of arsenic transmitted to the fetus, despite the administration of larger amounts of arsenical than those given in the present experiments.

In the human being, Kraul and Bodnar (1926) found that in a series of four pregnant women who had received neoarsphenamine therapy and subsequently expelled fetuses at various stages of pregnancy, there was arsenic in three fetuses which were born in the latter part of pregnancy, but none was present in a fetus extruded at six months. The passage of the drug or some of its decomposition products to the human fetus was also demonstrated by Eastman and Dippel (1933), who recovered small amounts of arsenic from the meconium of newborn infants whose mothers had received antisyphilitic treatment during pregnancy.

The statistical analysis of McKelvey and Turner (1934) has shown that in pregnancy the last trimester is clinically the most important period for arsenical therapy, and that even a few treatments in the last weeks preceding delivery will materially improve the chances for a healthy child. A relatively small amount of arsenical affords the fetus better protection against syphilis when the drug is given late in pregnancy than when it is given only at earlier stages of gestation. In the human being we have been able to discover no data regarding the quantity of arsenic which is transmitted to the fetus at various stages of pregnancy. The increase in therapeutic efficiency of the arsphenamines as pregnancy progresses suggests, however, that there is a correspond-

ing increase in the amount of arsenic which is transmitted to the human fetus as term is approached, similar to that which has been demonstrated in the rabbit.

Examination of the placentas revealed that a vastly greater amount of arsenic is retained by this organ than is transmitted to the fetus one hour following injection at full term. The average concentration of arsenic in the placenta was 175 times as great as that in the fetus, and the total arsenic content of the placenta was 18 times as great as that of the fetus.

Gradual liberation to the fetus of the arsenic stored in the placenta is revealed by the higher level of the drug in the fetuses twenty-four hours after injection than after one hour.

In the rabbit the complete separation of the fetal portion of the placenta from the maternal portion is readily accomplished, thus permitting accurate comparison of their respective stores of arsenic. The fetal portion contained, on an average, a total amount of arsenic six times as great, and a concentration twice as great, as that of the maternal portion. Previous investigations of the distribution of arsenic in the human placenta (Dejust and Vignes, 1925; Eastman, 1931) showed similarly a greater retention of the arsenical by the fetal portion, although results in the human being are complicated by the failure to attain complete separation of the two portions of the placenta, as well as by the variations among the specimens with respect to dosage and the time interval which elapsed following injection.

The storage of arsenic in greater concentration in the fetal portion affords an interesting contrast to the distribution of glycogen in the placenta, since glycogen is restricted to the maternal portion (Loveland, Maurer, and Snyder, 1931).

In the placenta, in contrast to the fetus, the variations in the total content and concentration of arsenic were not related to the stage of pregnancy. Similarly, no correlation was noted between placental arsenic, on the one hand, and the size of the litter, weight of the placenta, or total amount of neoarsphenamine injected, on the other. Since no attempt was made to wash the placentas, the unequal amounts of residual blood were taken into consideration as a possible source of the variations. However, the arsenic content of the blood one hour after injection has been shown to be sufficiently low, even when much larger doses of neoarsphenamine are employed (Voegtlin and Thompson, 1923; d'Haenens, 1925; Speert, 1937), so that differences of as much as 1 c.c. in residual placental blood, estimated to be the upper limit of variation, are inadequate to account for significant differences in the data. Probably of greater importance in this regard is the variable degree to which placentas in the later stages of pregnancy show regions of necrosis, infarction, and scarring, structural changes which alter the amount of functional tissue available for arsenic retention.

The present experiments throw light upon the mechanism of the anti-syphilitic effect upon the fetus of prenatal arsenical therapy. Although Underhill and Amatruda denied that placental transmission of the drug to the fetus is sufficiently great to be of importance in therapy, our

findings indicate that in the fetus there is a concentration of arsenic which is comparable to that in the maternal tissues. It may be inferred, therefore, that there is sufficient arsenic in the fetus to be an effective therapeutic agent. The arsenic concentration of the maternal tissues was calculated from data obtained by Voegtlin and Thompson (1923). In rats injected with a considerably larger dosage of neoarsphenamine than that given in the present experiments, these authors found an average excretion of 88 per cent of the administered arsenic in twenty-four hours. If one accepts this rate of excretion as applying for rabbits, the concentration in the maternal tissues twenty-four hours following injection is only twice as great as the maximal arsenic concentration in our series of fetuses. The placenta shows an average arsenic concentration 18 times as great as that of the maternal tissues.

In summary, there is evidence that a single injection of a therapeutic dose of neoarsphenamine administered near term results in a concentration of arsenic in the fetus and in the placenta, which is sufficient to exert an antisyphilitic effect. In explanation of the greater therapeutic efficiency of a given amount of arsenical, as measured by its ability to insure the birth of a nonsyphilitic offspring, when the drug is administered during the last trimester of pregnancy in contrast to earlier stages, it may be pointed out that as term is approached increasingly larger amounts of arsenic are transmitted to the rabbit fetus, as demonstrated in the present experiments.

It is interesting to note that the stage of pregnancy at which arsenic is first transmitted across the placenta of the rabbit, namely, about the beginning of the latter half of pregnancy, corresponds to the earliest stage of gestation in the human being at which the *Treponema pallidum* is found in the fetus (Hoffmann, 1936). The failure of substances as diverse as a chemical compound and a living microorganism to be transmitted to the fetus during early pregnancy, in contrast to later stages, illustrates the profound alteration in placental function which occurs as pregnancy progresses.

CONCLUSIONS

1. Placental function, as measured by the capacity of the placenta to transmit arsenic from mother to fetus, varies with the stage of pregnancy, the rate of transmission increasing as pregnancy progresses.
2. In a series of rabbit fetuses examined one hour following injection of the mother with neoarsphenamine, no arsenic was detected until the period of viability was approached; in a second series, examined twenty-four hours following injection, arsenic was found in the fetus as early as the beginning of the latter half of pregnancy.
3. The placenta contained much more arsenic than the fetus; the average arsenic content of the placenta was 18 times, and the arsenic concentration 175 times, as great as that of a fetus at full term one hour following injection.
4. The fetal portion of the placenta contained 6 times as much arsenic as did the maternal portion; the concentration of arsenic was only twice as great in the fetal as in the maternal portion.

5. Variations in the arsenic content of the placentas could not be correlated with the stage of pregnancy.

6. Gradual liberation of arsenic from the placenta to the fetus is indicated by the consistent finding of a greater amount of arsenic in the fetus twenty-four hours after injection than after one hour.

7. The concentration of arsenic in the fetus near term approaches the level calculated to be present in the maternal tissues when definite anti-syphilitic effect is exerted.

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THE DIET OF THE PREGNANT WOMAN*

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STUDIES of the basal metabolism of pregnant women have shown that it tends to fall very slightly during the first months, being, according to Root and Root, 1.5 per cent below the Harris-Benedict standard for a woman of the same height and weight in the fifteenth week. Thereafter, it steadily rises until a few days before delivery, when it is about 23 per cent above that of five months earlier. The gain in weight during pregnancy approximates 14 per cent. An increase in metabolic rate corresponding to increase in weight would result in an increase in metabolism of only 5 per cent, instead of the observed 23 per cent. It is evident, therefore, that the fetal tissues and their adnexa have a higher specific metabolism per unit of weight than that of the unincumbered woman.

All authorities are agreed that the pregnant woman requires for her nutrition nothing other than those nutrients which she requires in the nonpregnant state, but that she needs more of everything, but particularly more energy, protein, calcium, phosphorus, iron, and

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the vitamins. The more recent contributions to our knowledge of the nutrient requirements of the expectant mother, and considerations affecting her utilization of food substances, present some interesting viewpoints of great practical importance. They reveal certain aspects of maternal nutrition which require special attention, and errors which may have grave consequences, but which may, in most instances, be avoided by wise management.

Provided no conditions arise which interfere with digestion and absorption there is no special problem in pregnancy arising in relation to the protein moiety of the diet. The proteins should have high biologic value, and this is easily attainable by the inclusion of suitable amounts of milk and meats, since the proteins of these foods supplement well those of cereals and other vegetable foods and increase the utilization of the latter. When pregnancy is complicated by frequent vomiting, the amino acid needs of the woman will not be satisfactorily met, however satisfactory may be the quality or quantity of her food proteins. The same may safely be said regarding any other dietary essential. In calling your attention to certain experimental and clinical observations bearing on the nutrition of the pregnant woman, my objective is to bring together for your consideration ideas which are new and which further study may show to require revision or modification, but which have sufficient basis for confidence, both in animal experiments and clinical observations, to warrant careful attention by clinicians.

THE MINERAL ELEMENTS

Calcium and Phosphorus.—Macy and her co-workers (1930) made quantitative studies on the calcium and phosphorus balances of three women, and found that one experienced considerable losses of calcium at the twenty-sixth and thirtieth weeks of gestation; another at the fourteenth week, and a third at the thirtieth and thirty-fourth week, although their usual home diets were abundant in all known food essentials. Phosphorus retention appears from their data to have been more satisfactory than that of calcium. Sherman (1932) and Schmidt and Greenberg (1935) estimate the average daily calcium intake of American women to be 0.063 gm. The average daily calcium intake of the women studied by Macey and co-workers was 1.735, 1.97, and 2.09 gm., and of phosphorus, 2.25, 1.70, and 2.46 gm., respectively. The ratio of Ca:P in these diets was 1:1.3, 1:0.86, and 1:1.17. In absolute amounts of these elements, these diets were undoubtedly sufficient. If we may judge of human requirements by those of the rat, it appears from the studies of Cox and Imboden (1935) that a ratio of Ca:P of 1 is near the optimum, when the calcium level is 0.49 per cent of the diet. They tentatively place the calcium requirement of the human adult at 1.37 gm. An excess of phosphorus is better tolerated than an excess of calcium.

There are several factors which influence calcium and phosphorus metabolism. One of these is worry. Macy found that a woman who

suffered anxiety at one period during pregnancy went into negative calcium balance at that time. It is well known that vitamin D is extremely important in conditioning the body to utilize both of these elements, and more particularly phosphorus. If the diet of the pregnant woman contains sufficient milk and green vegetables, she will secure sufficient of both of these elements. She will not, however, utilize these properly, unless the remainder of her diet be properly constituted, as will be presently shown.

Iron.—Our views concerning the utilization of iron in nutrition have undergone significant changes in recent years. There is abundant evidence that deficiency of this element is widespread. I shall not discuss anemias other than that form for which idiopathic hypochromic anemia has become the term of choice. This is a simple secondary anemia in which the reduction in hemoglobin greatly exceeds that of the red cells. It is likely to occur in any individual who suffers from gastric anacidity, and is frequently encountered during pregnancy. Strauss (1934 and 1936) has given an excellent discussion of this condition. He points out that gastric digestive defects, in association with fetal demands for iron, may be the cause of this anemia, and that it can be relieved or avoided by the administration of generous amounts of iron. He recommends 0.5 gm. daily of ferrous sulfate for this purpose.

In this connection I should mention the importance of selecting the best form of iron compounds for therapeutic use. Simmonds, Becker, and McCollum (1927) showed that the inclusion of 0.2 per cent of ferrous sulfate in the diet of the rat causes almost, if not quite, complete destruction of vitamin A. When this salt is added to butter fat or cod liver oil, these fats very quickly become rancid, and the destruction of vitamin A is catalyzed. No such effect is produced by ferric citrate, hence, I would suggest that a ferric salt be used instead of a ferrous salt. Elvehjem and co-workers (1933) have recommended ferric pyrophosphate as a salt having almost ideal properties for therapeutic purposes, since it is readily absorbed, and is the least astringent of iron salts commonly available.

Until recently it was believed that the total iron content of ordinary foods is available for utilization by the body. The introduction of the new dipyriddy reagent by Hill, which differentiates between the so-called "hematin" iron and other forms of iron, and extensive studies at the University of Wisconsin, by Elvehjem (1933), has brought to light the fact that only about 50 per cent of the iron in such common foods as wheat, oats, and yeast, is available physiologically. The body's daily requirement for iron has for years been assumed to be about 15 mg. for the unincumbered adult, and for the pregnant woman the figure has been set at 20 mg. or above. But since the iron of foods is by no means all available, the actual requirement for iron becomes problematical.

Further light has been thrown on this subject by recent researches. Mettier (1930) found that certain anemic patients did not respond to iron therapy, but did so readily when iron was provided along with a

diet containing an abundance of fresh fruits and vegetables. In fact the anemia accompanying scurvy is, he states, relieved by such a diet. This would seem to indicate that ascorbic acid is in some way necessary for iron utilization. That this may be the case is shown by a study reported by Dunlop and Scarborough (1935) on a scorbutic man. He had eaten bread, syrup, margarine, corned beef or smoked sausage, cheese, and tea made with sugar and canned milk, during a year and a half. During this period he had taken no fresh vegetable foods, potatoes or fresh milk. His iron intake was estimated at 10 mg. per day, or two-thirds the assumed requirement. He was kept on his usual diet and given 60 mg. daily of ascorbic acid. Blood corpuscles increased during seventeen days from 2,050,000 to 4,226,000, and the hemoglobin from 45 to 77 per cent. After this he was continued on his usual diet, but no more ascorbic acid was administered, yet in eleven weeks the corpuscles increased to 5,600,000, and the hemoglobin to 100 per cent. They conclude that vitamin C deficiency may be a factor contributing to the development of anemia, even in the absence of clinical signs of scurvy. The studies referred to point strongly to undernutrition as respects ascorbic acid, as a possible cause of anemia in pregnant women. Clinicians should extend our knowledge in this direction.

Iodine.—The excellent studies of Marine, Kimball, McClure, and Olin, in Michigan and Ohio, which are endemic goiter regions, have shown beyond question the importance of keeping the thyroid glands of pregnant and lactating women saturated with iodine. Writing in 1935, McClure, of the Henry Ford Hospital, said:

"In Michigan iodized salt was introduced through the grocery stores by the efforts of the Pediatric Section of the Michigan State Medical Society in 1924. The results in Detroit and Southern Michigan which we have studied have been astounding, as viewed from the number of enlarged thyroids among the school children and also the number of patients coming to operation for the three types of goiter—colloid, adenomatous, and hyperplastic. In 1924 the survey of Kimball in different parts of Michigan showed a very high incidence which has always been endemic here. In Detroit it was not as high as in other parts of the states, but even here there was an incidence of 35 per cent of enlarged thyroids in the school children. In the eleven years that have passed, this incidence has gradually decreased until now less than 1 per cent of our school children have enlarged thyroids. After two years with the use of this salt the number of goiter operations in the seven largest hospitals in Southern Michigan began to decline, but the total of all operations showed but little change. The following conclusions are reached from our studies here:

1. Iodized salt as used in Michigan did, at first, apparently increase the number of thyroid operations.
2. The increase was in the nodular goiter or adenomatous group, and, we believe, the iodized salt may have activated a group of quiescent adenomas, producing toxic goiter symptoms.
3. The increase reached its peak in the second year after the introduction of the iodized salt.

4. An increase in the death rate from goiter as shown by the Board of Health statistics reached its peak in the second year after the introduction of iodized salt.

5. There was no increase in hyperthyroidism, excepting in the nodular or adenomatous group.

6. The number of operations for toxic diffuse and toxic nodular goiter has rapidly and steadily decreased after the apex of the second year increase had been reached.

7. The incidence of endemic goiter or enlarged thyroid has been reduced almost to nil since iodized salt has been so widely used.

8. We now see no cases which show the slightest ill effects from the use of iodized salt.

9. Toxic nodular goiter and toxic diffuse goiter are less likely to occur when there has been no previous enlargement of the thyroid (endemic goiter); at least this would seem a safe conclusion based on our experience."

The Vitamins.—Vitamin A is now a familiar substance, having been prepared in the crystalline state by Holmes, and also as its precursor, carotene, the yellow pigment of many yellow fruits and vegetables. A deficiency of this vitamin causes keratinization of epithelial tissues throughout the body. Keratinized epithelium tends to desquamate and form foreign bodies at any site where it occurs. Relatively severe depletion of the body of this nutrient causes depletion of the retina of visual purple, with consequent loss of acuity of vision in subdued light; a high incidence of cystitis and of kidney stones; invasion of the respiratory tract by microorganisms which produce purulent accumulations, and cause a high mortality from respiratory infections.

In human subjects such degrees of depletion are common in certain parts of the world, but are rare in America. Much confusion now exists on the point of the extent and seriousness of vitamin A deficiency here. The test for disadaptation of the eyes as a sign of incipient vitamin A deficiency, introduced by Jeans, has all but been discredited by other workers. All that can be safely said at present is that vitamin A deficiency is not uncommon in man in certain places, and that even incipient keratinization of epithelium should, by all that we know, be a menace to health. Mason's observation that senile vaginitis responds to vitamin A therapy, points strongly to the belief that even the American diet may in many cases induce deficiency. The studies on student groups and industrial groups, in which a dietary supplement was given one group, and an unsupplemented group served as controls, seem to establish, that whereas the provision of an abundance of vitamin does not reduce the number of colds per person per year, it does reduce both their severity and duration. The ease with which it can be demonstrated that the enamel of the teeth can be made hypoplastic in experimental animals by a degree of deficiency of vitamin A which does not reveal itself in other symptomatology, further supports this conclusion.

Vitamin B₁ (Thiamin).—There is much evidence that deficiency of thiamin is widespread among American people to a degree which brings about a borderline state of malnutrition as respects this factor. Cowgill (1934) after an extensive study of the thiamin content of many dietaries, recommends to physicians the consideration of thiamin therapy in gastrointestinal disorders, heart disorders, various neurologic conditions, anemias, infant nutrition, anorexia, restriction of growth, and in conditions of heightened metabolism.

Since anorexia is the earliest symptom of thiamin deficiency, voluntary restriction of food consumption is likely to occur, as has been pointed out by Minot, Strauss and others. Strauss and McDonald (1933) appear to have afforded convincing proof that the multiple neuritis of pregnancy is not the result of some occult toxemia, but is due to thiamin deficiency. Women who vomit during pregnancy establish a vicious circle owing to impairment of digestion and absorption, even when the diet which is available is adequate. Berkwitz and Lufkin (1932) have reviewed the literature relating to 52 cases of polyneuritis of pregnancy and conclude: "The clinical and pathological picture of the nerve changes in pregnancy is the same as that resulting from alcoholism, infectious conditions, and diet deficiency disturbances such as beri-beri, and pellagra . . ." Since it is well established that thiamin plays a role in carbohydrate metabolism, and that in deficiency of this vitamin, pyruvic acid cannot be further transformed, and accumulates in the tissues, the suggestion of Plass and Mengert (1933), that the recent tendency to force a high carbohydrate diet on patients with vomiting of pregnancy would seem to increase the risk of producing vitamin deficiency, should be kept in mind. Thiamin is used up in carbohydrate metabolism, and the higher the intake of this moiety of the diet, the greater is the requirement for this substance. It appears probable that the convulsions which occur in thiamin deficiency are due to the accumulation of pyruvic acid in the brain. The significant fact which emerges from the observations cited, on the effects of thiamin deficiency, and of vomiting in pregnancy, is that prevention should be the watchword, and that all women should be educated to understand the importance of taking, before pregnancy occurs, and throughout gestation, a diet optimal in composition, so that the reserves of all the vitamins shall be high. It is suggested that a sound policy is the supplementing of the woman's diet at the outset of pregnancy, with yeast, wheat germ, yeast concentrates, such as Vegex or Marmite, or with appropriate doses of the crystalline vitamin, which is now available at relatively low cost.

Vitamin C (Ascorbic Acid).—It is not desirable here to attempt a review of the pathology of scurvy and of subclinical scurvy. It is well established by the work of Hojer, Wolbach, King and others, that deficiency of ascorbic acid impairs the faculty of the endothelial cells to produce and maintain intracellular matrix, and that hemorrhage is due to this impairment. Ascorbic acid has been clearly shown to play a role in one or more oxidation-reduction systems in the tissues, and when the tissue stores are reduced, oxidative processes are interfered

with. Ascorbic acid is likewise closely associated with the formation of complement in the blood, and the complement content falls a considerable time before signs of qualitative malnutrition are visible. King and his associates have shown that in guinea pigs with low ascorbic acid reserves, but showing no signs of scurvy, the injury which is caused by the injection of half of a minimum lethal dose of diphtheria toxin, or other bacterial poison, is extremely great as compared with animals whose reserves are high. Several other investigators substantiate this fact. Cotti and Larizza (1936) found that the provision of ascorbic acid reduces the blood coagulation time, a matter of great importance to the obstetrician.

Vitamin D.—Vitamin D was discovered in investigations made to determine the cause of rickets, for which condition it is a specific remedy. It maintains at the normal level the inorganic phosphate content of the blood, and also plays a role in maintaining normal calcium metabolism. In recent years vitamin D therapy has been employed therapeutically in a variety of conditions far removed from rickets. These cannot be reviewed here, but attention must be called to the view of Weld, that vitamin D is of even greater importance in maintaining normal capillary resistance than is vitamin C. The observations of Richardson (1934) deserve special mention.

Richardson reported a study of the effect of viosterol during pregnancy on the duration of labor, which should be extended by other obstetricians as soon as possible. The combined duration of labor of 132 primiparous patients who had taken viosterol during pregnancy, totaled 792 hours, or an average of six hours per patient, which, he states, is about one-third the duration of the first normal labor. In his practice the combined duration of labor in 63 primiparous patients who were not given the vitamin totaled 1,197 hours, an average duration of nineteen hours. In a series of multiparous patients who received viosterol during pregnancy, who were not compared with a series of untreated controls, the average duration of labor was 3.5 hours.

Wilder and Howell point out that the majority of human patients with parathyroid enlargement occur in the northern part of the United States, where there is a deficiency of sunshine. The action of ultraviolet rays upon the skin causes the formation of one of the forms of vitamin D. Several investigators have described the extraordinary enlargement of the parathyroid glands in chickens which are deprived of vitamin D and of sunlight. The significance of the parathyroids, in the maintenance of normal calcium metabolism and the onset of tetany, when there is a deficiency of the parathyroid hormone, lends great weight to the suggestion that a satisfactory supply of vitamin D may be of profound significance to the health of the pregnant woman.

Milk Fever.—The tetanic seizures characteristic of so-called milk fever in cows, and of "lambing sickness" in ewes, is now well known to be due to hypocalcemia, and is the analogue of tetany in infants brought about by low blood calcium. It is prevented by feeding a

ration sufficiently rich in calcium, and by nutritional management which safeguards the body mechanisms associated with calcium metabolism. It occurs in animals at the outset of lactation, or during early lactation, for the reason that there is then an enormous output of calcium in the milk. If the body's reserves of this element, and the amount in the food are low, the blood calcium falls to the tetany level. The condition responds readily, in most areas, to the injection of calcium gluconate, and is prevented by a high calcium ration. Vitamin D would also be of importance. In a few areas where the soils are deficient in magnesium, the so-called "grass tetany" occurs, which is due to low blood magnesium.

An analogous condition appears to occur in certain women, although the disease has not been studied effectively in human patients. These conditions are mentioned here because they suggest a field of investigation for obstetricians.

In this brief discussion I have attempted to call attention to the more important conditions in which obstetricians are interested, in which the state of nutrition of the expectant mother may be safeguarded by careful attention to the diet. In all normal cases, her nutrition will be adequately met, provided she takes a diet built up around sufficient amounts of what I have called the protective foods. These are milk, green and yellow vegetables, fresh, uncooked fruits, and a moderate consumption of meats. It is not necessary here to particularize as to the special properties of these foods, and their supplementary relations. It is believed that in many instances the expectant mother suffers in health because of too great restriction of her diet to refined cereal foods, manufactured dry food products such as are offered in great numbers in stores, the fats of which are often somewhat rancid, and of sugar. The specific relations which have been mentioned between depletion of the body in respect to particular nutrients, and specific symptoms frequently encountered, are called to attention as evidence that the diet of the pregnant woman in America requires the attention of her physician, and that effective dietetic management should be given to these women as a feature of obstetric practice.

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DISCUSSION

DR. A. T. MILHORAT (by invitation).—The need for increased amounts of nutrients during pregnancy is suggested by the increased respiratory metabolism of the expectant mother and the requirements for growth of the fetus. This increase in the total respiratory metabolism, as has been shown, is greater than the increase in body weight. We know from the studies of Carpenter and Murlin (*Arch. Int. Med.* 7: 184, 1911) that the basal metabolism of the expectant mother just before delivery is the same as that of both mother and child just after parturition. The increase in the surface area of the pregnant woman is much smaller than is the increase in her metabolism. Since the heat of the organism must be dissipated through this surface, the relatively greater increase in the total metabolism will result in a rise in the skin temperature. This would explain the feeling of warmth which many pregnant women experience, and their ability to withstand low environmental temperatures with comfort.

The need for increased amounts of calcium and phosphorus during pregnancy is evident. Many normal persons have intakes of these minerals that are barely adequate. Hence, during pregnancy, with its extra demands, the intake is likely to be deficient unless more calcium and phosphorus are ingested.

Dr. McCollum has emphasized, very wisely, the need for increased amounts of vitamin B in instances where large amounts of carbohydrates are given. In women suffering from prolonged emesis, the ingestion and absorption of vitamin B are likely to be impaired. The administration of large amounts of carbohydrates will increase further the needs of a patient whose requirements due to her pregnancy are already great, but whose intake of the vitamin is deficient. The appearance of polyneuritis in these patients should be watched for carefully. It is well to remember that the subjective symptoms of the patient, namely, numbness and tingling of the fingers or toes, appear much earlier and therefore are more valuable for making a diagnosis of polyneuritis than are the findings of sensory defects on neurologic examination. The development of numbness and tingling in such patients should suggest the diagnosis of polyneuritis, and the parenteral administration of vitamin B should be considered.

The tachycardia often observed in patients with gestational polyneuritis may in many instances be due to the same factors as in beriberi. Weiss and Wilkins (*J. A. M. A.* 109: 786, 1937) have shown that the so-called beriberi heart is not uncommon among persons whose diet has been deficient in vitamin B. How often this occurs in pregnancy I do not know, but the likelihood of its occurrence should be borne in mind.

One result of a deficiency of iron easily demonstrated, is the development of a hypochromic anemia. However, another result, that of an inadequate reserve of iron in the infant, is more obscure in its manifestations. Infants born of mothers whose intake of iron had been deficient usually have no anemia at birth but develop anemia within a year unless iron is administered.

The position of the proteins in the dietary management of the expectant mother is still somewhat obscure, but it is likely that more attention will be paid to these important foodstuffs as time goes on. The facts as given in the medical literature at present are these. During pregnancy there is a positive nitrogen balance. Furthermore, the retention of nitrogen during pregnancy is greater than that required for the fetus and adnexa. Under favorable circumstances, therefore, pregnancy is a period of nitrogen acquisition for the mother. For several years I have been interested in the problem of the protein metabolism during fasting and in pregnancy. It appeared of interest to know what influence pregnancy would have on the output of nitrogen during the fasting state. Would the pregnant organism in its need for nitrogen be able to manage its protein budget so that less nitrogen would be excreted? The results surprised me. During pregnancy the nitrogen excretion of the fasting bitch was at least 50 per cent higher per kilogram of body weight than during the nonpregnant state. Therefore, fasting during pregnancy represents a period of excessive destruction of the maternal proteins. A likely explanation is this: The protein molecule cannot be transported as such from the maternal to the

fetal structures. It must be broken down into the amino acids and resynthesized into the fetal proteins. The composition of the fetal proteins, however, is different from that of the maternal proteins; different combinations of the nondispensable amino acids are required. Hence, to supply the necessary amounts of the nondispensable amino acids, more maternal tissue is broken down than is used in the actual synthesis of the fetal proteins. The excess portion of the protein is catabolized, and the nitrogen is excreted in the urine.

Furthermore, animals which were able to withstand repeated fasts of thirty to forty days during the nonpregnant state without harmful effects, did poorly when fasted during pregnancy. Within six or ten days the fasting pregnant animal became nauseated, lethargic and weak. Often delivery was premature, with a high mortality among the newborn. Animals previously fed on highly nutritious diets withstood the fast better than those whose previous diet had been adequate but not especially rich in proteins and vitamins. These findings suggest the need for adequate amounts of proteins of high biologic value during pregnancy. Moreover, it would appear that protein deprivation in this condition very likely will have harmful effect.

In contrast, simple substances such as calcium and phosphorus are readily transferred from the maternal to the fetal tissues. This transfer is economically accomplished and no increased amounts of these minerals are lost in the excreta.

While the average normal woman might be able to go through the reproductive cycle without particular attention to the dietary demands, it is likely that skillful dietary management often is of value to the expectant mother in whom complications are likely to arise. The early months of pregnancy so often associated with vomiting and nausea are frequently a period of inadequate intake of dietary essentials. It is during the next few months, which represent the so-called silent period and which precede the months during which complications are most likely to occur, that the diet can be carefully regulated. The avoidance of any dietary deficiency, however slight, and the adequate storage of all essentials that the body can store might prevent the occurrence of a condition which would precipitate a more serious complication. Moreover, should a complication arise it is possible that the prognosis will be influenced by the previous dietary management of the expectant mother.

DR. ALFRED C. BECK.—For a number of years I have been trying to do some of the things which Dr. McCollum's presentation indicates. By giving a more balanced diet and, particularly, one in which the vitamins and minerals are ample, I believe that my patients have been freer from that condition which we call toxemia than they formerly were. Perhaps, it may be shown that the symptoms of the so-called toxemias are in reality evidences of a deficiency disease.

We all know that pregnant women have enormous appetites and that they overeat and usually gain excessively in weight. In this connection, I would like to ask Dr. McCollum if the tendency to overeat is due to an attempt on the part of Nature to satisfy the requirements of pregnancy by taking larger and larger quantities of highly refined articles of the ordinary diet which are deficient in some of the rarer but necessary elements.

DR. HENRICUS J. STANDER.—A great deal has appeared in the literature on the value of vitamin D in the utilization of calcium. As to whether there may be an excessive deposition of calcium in the fetal bones is an important question and there is some recent evidence in its favor. If this is so, it is possible that too much calcium may do harm, and particularly is that true of viosterol, vitamin D, in the utilization of calcium. I think that we should be a little hesitant about experimenting with the object in view of decreasing the period of labor by the use of vitamin D.

In the reference to milk fever, I think Dr. McCollum had in mind what is known as "parturient paresis" in cattle. Harding, Murphy and Downs of Toronto have shown that parturient paresis is due to a deficiency of glucose or in other words, to a hypoglycemia, rather than to a calcium deficiency. The cure of parturient

paresis in cattle at first consisted in the use of a pump to the udder, stopping the excretion of milk; later by giving glucose solution intravenously. Parturient paresis was noted particularly in cattle that were secreting large amounts of lactose, or milk.

I cannot fully agree with Dr. Milhorat on the subject of nitrogen metabolism, although, it is possible that by his recent work he can disprove some of the older views. Hoffström and Bar have shown that in the first third of pregnancy there is a negative nitrogen balance. Bar tried to show that the vomiting of pregnancy, particularly the gastrointestinal upsets observed in dogs, is associated with a nitrogen negative balance. In the second half of pregnancy there is a positive balance. One often sees a pregnant woman, who has been starved and whose weight at term is less than her nonpregnant weight, and yet the offspring is of normal weight.

Another of the important points mentioned by Dr. McCollum was the use of vitamin B₁ in the utilization of carbohydrate, and certainly in our treatment of the vomiting of pregnancy. It is quite conceivable that we could get better results if we paid attention not only to the glucose therapy advocated by Titus and others, but also to the importance of this second factor, namely, vitamin B in the utilization of sugar.

DR. MCCOLLUM (closing).—Dr. Beck asked me a question on which we have only a very limited basis for formulating an answer. The only studies with which I am familiar on the question as to whether a creature eats more of something that it does not need in order to get enough of something it does need, were made about twenty years ago by Osborne and several others. They concluded at that time that experimental animals eat for energy, and that when their energy requirement is satisfied, they stop, even though they need something they do not have in sufficient amount.

The point was raised that it might be hazardous to give women vitamin D during pregnancy. The difference between the therapeutic dose of vitamin D is less than the dose which has been demonstrated to produce toxic effect by many thousand times. The prophylactic dose for infants and children is four hundred international units a day, the equivalent of one teaspoonful of cod liver oil, which would be safe.

In regard to milk fever, I have the impression that there were cures of this condition by the use of calcium salts other than gluconate. In the dose which is given to an animal weighing perhaps 1,000 pounds, it seems inconceivable that the amount of carbohydrate equivalent in gluconic acid would go far in restoring low blood sugar. I think that is a blood calcium deficiency.

Mohr, Harold: The Pathogenicity of the *Trichomonas Vaginalis*, Ztschr. f. Geburtsh. u. Gynäk. 115: 115, 1937.

Mohr found that 55.2 per cent of women with a normal vaginal mucosa were trichomonas carriers. None of these women had any symptoms. On the other hand, 29 per cent of the women examined had typical trichomonas discharge, itching, etc., but were found to be free of trichomonads. This, to the author, was adequate proof that there is no specific pathogenicity. He found that there are no specific bacteria accompanying the organism. The *Trichomonas vaginalis* does not ferment dextrose and causes no change in the glycogen contents of the mucosa. The organisms will survive a pH of 4.0-7.0; they were found in a pH of 5.2-5.8 in 65 per cent of the cases.

EUGENE S. AUER.

RHYTHMIC CHANGES IN THE SKIN CAPILLARIES AND THEIR RELATION TO MENSTRUATION*

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INTRODUCTION

THIS present study was undertaken to determine the peripheral vascular changes, particularly those in the skin capillaries, in association with the menstrual rhythm, which is fundamentally a vascular phenomenon. The investigation of the peripheral vascular system was carried out by means of the production of capillary hemorrhages. Petechial or capillary hemorrhage has been studied with respect to many diseases and conditions. H. W. Jones and Tocantins in 1933 presented an historical account of the methods employed. As they stated, Koch in 1889 first tested the capillary resistance by means of intradermal punctures with a needle. The well-known tourniquet test and similar tests were suggested by Weill, Rumpel and Leede, and Frugoni and Guigni in 1911. Jones and Tocantins (1933) described another method of studying capillary hemorrhage, namely, the "flicking" test. The first suction method of testing capillary hemorrhage was described by Hecht (1907).

METHODS

The suction or negative pressure method used in the present experiments is based upon the application of a degree of vacuum adequate to produce capillary hemorrhage in the skin. The instrument was devised by Cutter and Johnson (1935) and has been called a capillary hemorrhage instrument (Fig. 1). This instrument is most satisfactory because frequent and accurate measurements can be made. It is readily adapted to clinical use since it is portable. Any desired negative pressure can be produced down to approximately 1 mm. of absolute vacuum as indicated by Cutter and Johnson (1935). The desired pressure can be maintained at any level. The calibration is such that the negative pressure can be read similarly to barometric pressure, or as done in these experiments, from barometric pressure down to vacuum. Compensation has been made for the pulsatile effect of the pump and the changes which might occur upon application of the measuring chamber and upon opening the stopcock. The small aperture permits one to make numerous tests at one time in a small area.

The skin areas that are the most suitable from the standpoint of constant number and development of the capillaries are the cubital spaces and the infraclavicular regions. In order to obtain the most uniform results only one of these spaces was used during the experiment. In every instance multiple readings were taken at the same time in the same general area. Frequently tests were made in the other ac-

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ceptable areas as a control. The experiments have been in progress approximately one year. Readings were taken on every individual daily, every second day, or every third day.

The test is readily and simply performed. The suction chamber is applied to the given area for an arbitrarily chosen time of exactly thirty seconds. The final reading is taken when three, and only three, small punctate capillary hemorrhages are produced.

In this work no attempt has been made to determine and correlate all of the numerous associated or related factors, such as blood pressure readings, skin temperatures, seasons of the year, meteorologic rhythm, repeated blood and platelet counts, capillary pressures as determined directly, blood analyses for female sex hormones, epinephrine, cholesterol, carbon dioxide, etc. I realize that many significant

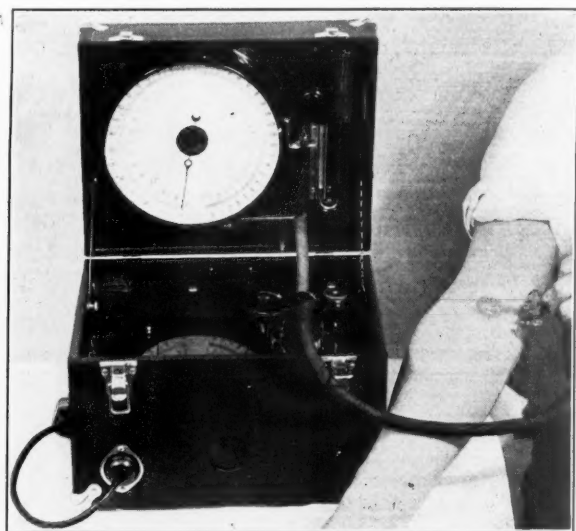


Fig. 1.—The Cutter-Johnson instrument is accurate and readily used clinically. Any desired negative pressure can be obtained and maintained. The site for the test and the method of application are indicated.

rhythmic changes do occur in the body. This paper is limited strictly to but one, the rhythmic changes in the skin capillaries as observed experimentally.

THE SUBJECTS

The total number of female subjects studied was 55. All were normal, healthy, working girls ranging in age from nineteen to fifty years. The menstrual cycles were normal in 40. The normal menstrual cycle has recently been demonstrated to have a wider range of variability than was formerly considered possible. Edward Allen (1933), Engle and Shelesnyak (1934), and others, including excellent summaries by Hartman (1936), Bartelmez (1937), and Ehrenfest (1937), have indicated that the normal cycle may vary four to seven days from the usually accepted normal of twenty-eight days.

Fifteen subjects had abnormal menstrual cycles. They were classified as functional amenorrhea; postclimacteric amenorrhea; amenorrhea resulting from hysterectomy; amenorrhea associated with pregnancy; and functional uterine bleeding.

The charts presented here are representative of the normal group. One chart of a subject with functional bleeding is included merely to demonstrate the variation from the normal. Along the horizontal plane of the charts the days are plotted. Along the vertical plane, the degree of vacuum necessary to produce capillary hemorrhage is indicated in millimeters of mercury. Menstrual bleeding is indicated by broken lines. During the time the subjects were on their yearly vacations, readings were not taken. This is indicated in each instance by interruptions of the graph.

SUBJECT 5.—Subject 5 is a normal individual, 34 years of age. She is 5 feet, 5 inches tall and weighs 125 pounds. Before puberty she was slightly overweight. Her weight became normal, however, at the age of twelve. Menstruation began at 12½ years of age. The cycles have always been of twenty-eight to thirty days' duration. The flow which is moderate lasts six to seven days. On the first day of flow she has cramps that occasionally are severe.

This subject was observed for seven menstrual cycles from April through October, 1937 (Chart 1). The menstrual rhythm is regular. The cycles were respectively of 31, 28, 30, 33, 26, and 34 days' duration.

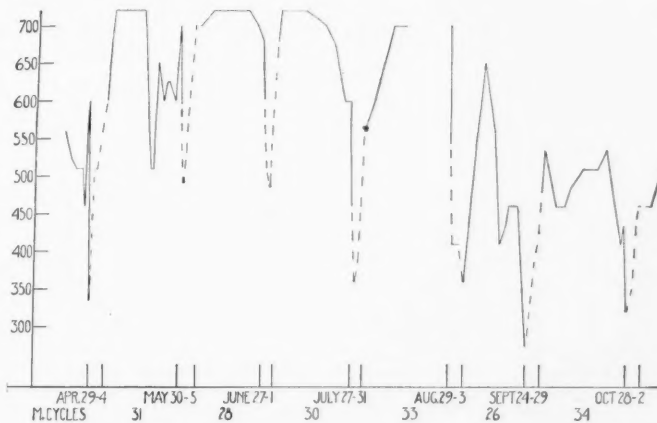
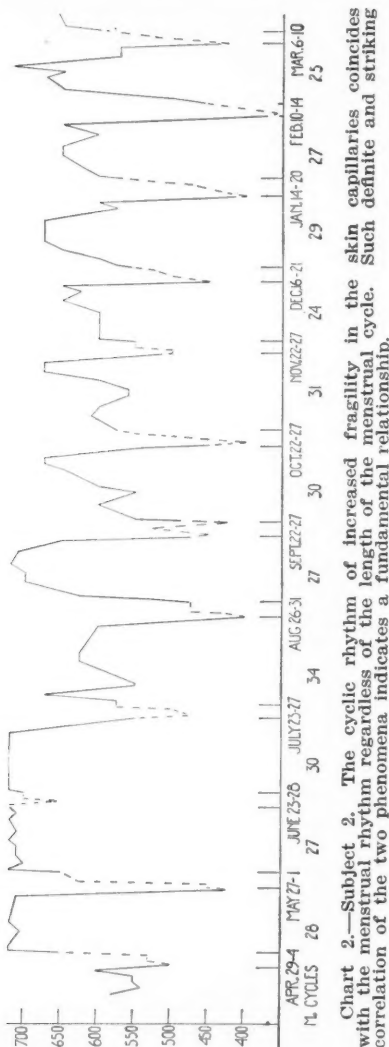


Chart 1.—Subject 5. The negative pressures necessary to produce capillary hemorrhage are indicated in millimeters of mercury on the vertical plane. During the first two days of menstruation an increase in capillary fragility is clearly demonstrated. There is also a moderate premenstrual increase.

In Chart 1 the typical reaction in the skin capillaries is demonstrated. The most frequent reaction noted is shown best in association with the menstrual flow beginning July 27. There is a gradual premenstrual decline in the degree of vacuum required to produce capillary hemorrhage. In this instance it was equivalent to 100 mm. of mercury. On the first and second days of the menstrual flow there is a sudden additional decline, equal here to 250 mm. of mercury. During the remainder of the flow capillary hemorrhage becomes more difficult to produce, so that within one to four days after cessation of menstruation the capillary fragility is at a level commensurable with that of the previous intermenstruum. Minor variations of this pattern or reaction are noted in conjunction with the flow of May 30. Here the entire premenstrual phase is accompanied by increased capillary fragility. Such reactions are described fully with the chart of Subject 18. Chart 1 clearly demonstrates that on the first and second day of every menstrual flow capillary hemorrhage is produced with greater ease than at any other time in the cycle.

During the intermenstruum a minor fall in the required pressure is frequently noted. The significance of this is not immediately apparent. On the whole the intermenstrual pressures necessary to produce capillary hemorrhage are relatively constant. During the months of September and October the general level is lower than that of the preceding months. Similar variations are noted in most of the subjects studied.

SUBJECT 2.—Subject 2 is 27 years old. She is 5 feet, 4 inches tall and weighs 125 pounds. Menstruation began with a profuse period at the age of 15 years. After the first period there was an amenorrhea of two months followed by a short period of time in which she flowed two or three times each month. At the age of 16 years the cycles became regular, occurring every twenty-eight to thirty days. The menstrual flow has always lasted seven days. This subject was underweight until the age of 22 years, when, following an appendectomy, her weight became normal.



This subject was under observation from April, 1937 through March, 1938, during which time 12 menstrual cycles were studied. The cycles were 28, 27, 30, 34, 27, 30, 31, 24, 29, 27, and 25 days in duration (Chart 2). In this subject, as in the previous one, capillary hemorrhage was produced with much greater ease on the first and second days of each menstrual flow. The differences in pressure readings were definite, in one instance being 275 mm. Premenstrual declines in pressure levels were the rule. Greater difficulty in producing capillary hemorrhage in the latter days of the menstrual flow was a constant finding, similar to that noted in the previous subject. The only exception was observed with the flow in September

which clinically was no different from the subject's normal flow. In this instance a secondary increase in capillary fragility occurred late in the period of flow.

The sudden fall in negative pressure invariably occurred in association with the flow regardless of the duration of the cycle. This is demonstrated in the cycles of thirty-four and twenty-four days' durations. The typical pattern of the normal reaction so far described is varied in one cycle in this subject. In June there was no increase in capillary fragility on the first day of flow. As noted on the chart, the fall in negative pressure did not occur until the third day and then was only 70 mm. This very meager reaction in the peripheral vascular system was associated with a very scant menstrual flow from the uterus.

During the intermenstruum in the May, June, and July cycles, capillary hemorrhage was difficult to produce and the level of pressure as shown on the chart was constant. In the months of August, October, November, and December the intermenstrual pressure levels were consistently lower.

SUBJECT 10.—Subject 10, aged 26 years, is 5 feet, 6 inches tall and weighs 117 pounds. Her weight has been normal throughout life. Menstruation began at the age of 15. Since the onset the cycles have been irregular, in that the flow occurred every two to four months. At one time there was five months' amenorrhea. The menstrual flow is moderate in amount and lasts seven days. Since the beginning of the present experiment in April, 1937, the cycles have been more regular and the duration of the flow has decreased to five days. The menstrual flow is moderate in amount the first three days and scant the last two.

During the last two years, two menstrual periods have been accompanied by severe menstrual cramps. With one of these she fainted. One occurred during this experiment. She is emotionally upset, nervous, and irritable before every menstrual period. Activity during this time relieves the symptoms.

The subject was observed from April, 1937 through March, 1938 during which time 10 menstrual cycles were studied. The cycles studied were more normal in regard to regularity of rhythm than the patient had experienced at any previous time. The cycles were, respectively, 59, 27, 28, 36, 34, 32, 31, 28, 49, and 28 days in duration (Chart 3).

In this subject regardless of the lengths of the cycles there was at the onset of menstruation a sudden fall in the negative pressure required to produce capillary hemorrhage. The pattern varied to some extent from that noted in the more normal individuals. Whereas the reaction in the more normal subjects as described above was typified by increase in capillary fragility on the first and sometimes the second days of flow, the increase noted here continued through the third day. This more slow response is consistent with the high and unusually constant level of capillary fragility noted throughout the year in this subject. In two instances (Chart 3, June 10 and July 8), there was no increase in the capillary fragility until after the first day of menstruation. This is an unusual finding. During the remainder of the flow the pattern duplicated the normal.

The menstrual flow of Aug. 13, 1937 was accompanied by a type of reaction in the skin capillaries that differed from the usual reaction observed in this subject. One week prior to the onset of flow a rapid decline in negative pressure occurred. This low level persisted through the first four days of menstruation without any additional drop during menstruation. Thus, the negative pressure remained at a constant low level for six days, unlike the findings in the other cycles of this subject. Associated with this varied pattern, the subject had a very profuse flow and a very severe dysmenorrhea. The significance of this is dealt with in the discussion.

Chart 3 shows that menstruation did not occur in January, 1938. Near the expected time of menstruation in January, the subject had all of the usual symptoms that precede menstruation. She stated she anticipated the flow within a day or two. Associated with these clinical symptoms of impending menstruation, there was a definite increase in capillary fragility. After several days, during which time the lower pressure level was maintained, the subject reported that the clinical symptoms were disappearing and that she did not think she would menstruate. In exact correlation with these altered symptoms the capillary fragility decreased and returned to a normal intermenstrual state without the occurrence of menstruation.

SUBJECT 18.—Subject 18, 28 years of age, is 5 feet, 2 inches tall and weighs 104 pounds. She first menstruated at 10½ years. The cycles have always occurred regularly every twenty-six to twenty-nine days. The length of flow is five to six days and is characterized by a sudden onset of brisk bleeding. After three days the flow diminishes gradually. Approximately one week before the onset of flow the breasts become markedly tender, the subject feels tense and becomes nervous and irritable. It is of interest to note that extreme physical work relieves these pre-menstrual symptoms to a large extent.

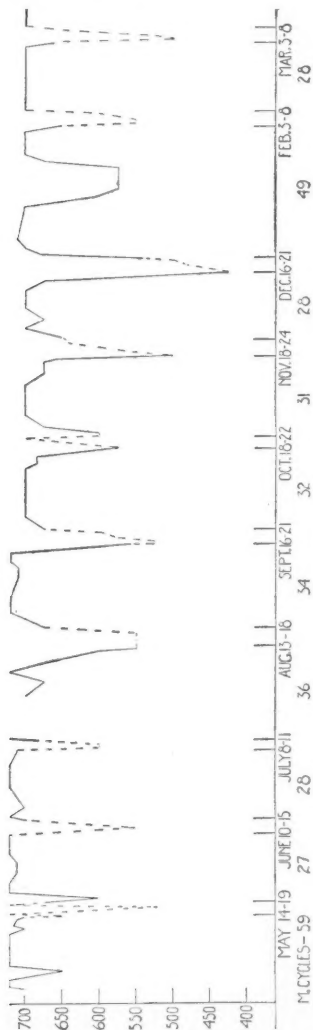


Chart 3.—Subject 18. The correlation of the rhythm in the skin capillaries and in menstruation is definitely shown. The January period was missed but the usual menstrual molimina appeared and disappeared simultaneously with the rhythm of increased and decreased capillary fragility. The prolonged period of increased capillary fragility associated with the menstrual flow of August 13 was accompanied by dysmenorrhea and a profuse flow.

Eleven menstrual cycles were studied in this subject from April, 1937 through February, 1938. The cycles varied from twenty-six to thirty-two days in duration (Chart 4).

During April, May, June, and July capillary hemorrhage was difficult to produce. During this time the reaction in the skin capillaries in association with menstruation was less profound. The subject stated that in these months the menstrual flow was much more scant than her usual normal. The remaining months of the investigation demonstrated a general lower level with wider ranges of variations in capillary fragility.

Typical findings at menstruation are exemplified during the flow of Oct. 3, 1937. The late premenstrual phase is accompanied by increased capillary fragility, and on the first day of flow a marked increase in fragility is noted. In the November, January, and February cycles a slight modification of this reaction occurred. The alteration in capillary fragility in the premenstruum took place several days before menstruation began and the increase in fragility was marked. In one instance it

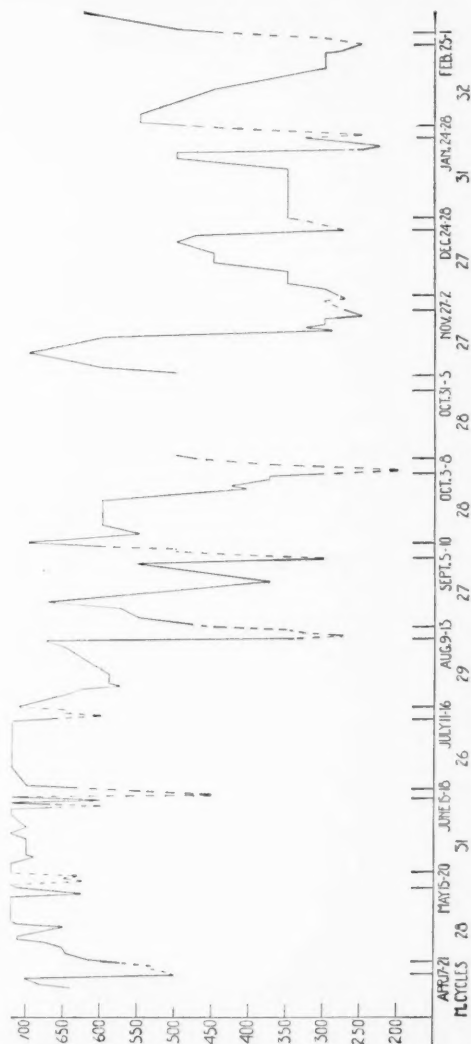


Chart 4—Subject 18. The rapid premenstrual changes in capillary fragility are associated with the appearance of menstrual menses and in two instances with slight uterine bleeding. Menstruation since August has been profuse. During the four previous months the flow was scant.

was equivalent to 300 mm. of mercury in twenty-four hours. In the three cycles mentioned the low premenstrual levels were maintained without any further significant changes in capillary fragility on the first day of flow.

With the marked increase in the ease with which capillary hemorrhage was produced a few days before the onset of menstruation on January 24, there was a slight uterine bleeding characterized as spotting. Likewise, just prior to menstruation on June 15, there was a premenstrual increase in capillary fragility associated with simultaneous uterine bleeding for three hours.

Exactly corresponding to the time in the premenstruum when skin capillary hemorrhages were produced with relatively great ease, this subject noted subjective symptoms of impending menstruation. The most intense symptoms were evident just before the menstruations of November 27 and February 25. These two periods were preceded by the most profound and prolonged increase in capillary fragility.

SUBJECT 30.—Subject 30, aged 27 years, weighs 107 pounds and is 5 feet, 6.5 inches tall. Before puberty she was underweight, but since then she has weighed as

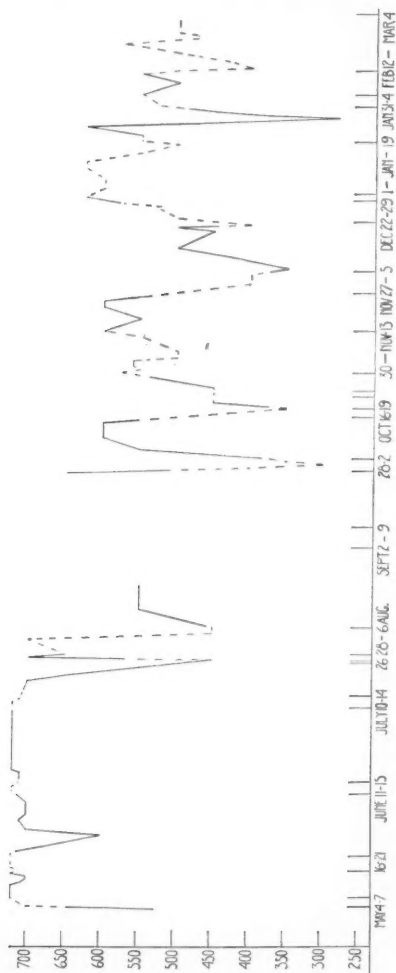


Chart 5.—Subject 30. There is no demonstrable cyclic rhythm in capillary fragility. The menstrual rhythm is entirely irregular. There is no correlation between the two phenomena in this subject with functional uterine bleeding.

much as 140 pounds. Menses began at 13½ years. The flow was regular every twenty-eight days and lasted four days until the age of 23. Since then she has been entirely irregular, having metrorrhagia and menorrhagia. With the abnormal bleeding, dysmenorrhea has been severe. Examination revealed normal pelvic organs.

This subject was observed from May, 1937 to March, 1938. The cycles were entirely irregular (Chart 5), in that the subject flowed both too often and too long. The menstrual flow of May 4, 1937 was accompanied by a decrease in the fragility of the skin capillaries, unlike that observed in normal menstruation. The uterine bleeding of May 16, June 11, and July 10 occurred without any variation in the

peripheral vascular phenomenon. On July 26, uterine bleeding was present for this one day only and was associated with an increase in capillary fragility. Two days later, however, menstruation took place irrespective of the state of capillary fragility of the skin capillaries. The pattern of reaction in the skin capillaries with the onset of menstrual flow on September 28 duplicates that seen in the normal subjects. In the group of functional bleeders, normal reactions interspersed among reactions at variance with the normal are observed frequently.

Through the remainder of the chart it is evident that there is no correlation between the skin capillary reaction and uterine bleeding. Endometrial biopsies taken at intervals reveal an endometrium without the influence of a corpus luteum.

SUMMARY AND DISCUSSION

In association with menstruation in the normal subjects studied, a fairly uniform series of events occurs in the skin capillaries. These events are variations in capillary fragility, or capillary resistance, or, as I prefer to designate it, the phenomenon of capillary hemorrhage.

In normal subjects on the first day of the menstrual flow, there is uniformly a considerable increase in ease of producing capillary hemorrhage. The changes in the required negative pressures occur with marked rapidity. Measured in millimeters of mercury indicative of the degree of vacuum required to produce the capillary hemorrhage, this marked and rapid change varies from 75 to 300 mm. In some instances the variation may be as great as 200 mm. of mercury within two hours. There is frequently a small additional increase in capillary fragility on the second day of flow. During the remainder of the menstrual flow the capillaries become more resistant. In other words, capillary hemorrhage becomes increasingly difficult to produce during the remainder of the menstrual flow. By the second or third day after the cessation of the menstrual flow, the negative pressures required to produce capillary hemorrhage reach a level approximately the same as that observed during the previous intermenstruum. As demonstrated in the charts, this pattern of reaction in the peripheral vascular system takes place at the approximate time of menstruation regardless of variations in the lengths of the menstrual cycles or menstrual flow.

During the late premenstrual stage there is usually a gradual increase in capillary fragility (Chart 1, July 27). In some instances the increase is relatively slight while in others it is great (Chart 4, November 27). As a rule the premenstrual change is followed by rapid increase in capillary fragility upon the first day of flow as noted above (Chart 1, July 27). Those instances which evidence continued low premenstrual readings are usually not followed by significant changes with the onset of menstruation (Chart 4, November 27).

Another modification of the demonstrable reaction in the premenstrual stage is concerned with a decreased capillary fragility one to three days prior to menstruation (Chart 4, August 9 and Chart 1, May 30). These variabilities in the type of reaction are not inconsistent with such a biologic phenomenon as menstruation.

Indicative of the fact that these skin capillary phenomena are associated with menstruation is the consistent regularity with which the two

occur together (Charts 2 and 3). Additional evidence is obtained from the demonstration that the sudden premenstrual increase in capillary fragility several days before the onset of menstruation is occasionally accompanied by slight uterine bleeding (Chart 4, June 15 and January 24).

Of importance in this respect is the direct correlation of the so-called menstrual molimina with the premenstrual phase of increased capillary fragility (Chart 4). Absolute proof that these two are directly associated is obtained in Subject 10. In this subject menstruation which was expected in January, 1937, failed to appear, but the skin capillaries evidenced the usual cyclic phenomenon that coincided with menstrual rhythm. In complete accord with the increase and then the decrease in capillary fragility at this time, menstrual molimina appeared and disappeared. Gebert (1936) reported the appearance of menstrual molimina in two instances of altered dermatographic latency time in the premenstruum.

In the intermenstruum, the negative pressures required to produce capillary hemorrhage may be relatively constant as noted in Subjects 5 and 10. On the other hand there are numerous instances in which there is a brief period of increased capillary fragility near the midpoint of the cycle.

In some subjects (Chart 4), the intermenstrual levels varied considerably during the course of the experiment. The general trend of the entire group is toward an increased fragility of the capillaries during the fall and winter months.

In Subject 10 the apparent high resistance of the capillary endothelium as indicated by the high pressures required to produce capillary hemorrhage, the lack of variations during the year of study, the delayed response on the first day of menstruation, and the continued but slight increase in capillary fragility extending through the third day of menstruation which is unduly long, suggest the fact that in this individual a corresponding resistance of the capillaries in the uterus or possibly their inability to adequately respond might explain the coexistence of amenorrhea.

Conclusive evidence that the phenomenon described is an integral part of normal menstruation is the demonstration that in association with abnormal or functional uterine bleeding this reaction is completely dissociated (Chart 5). Endometrial biopsies were studied as a guide to the character of the bleeding. In a later paper this phase will be fully elaborated upon.

That capillary hemorrhage is produced experimentally with greater ease at the time of menstruation has been reported by Stephan (1921). In studying various diseases by means of the Rumpel-Leede phenomenon, he observed that the phenomenon was likely to be positive in women during menstruation. Seyderhelm and Heinemann (1930) described similar findings. Pistor (1935) stated that petechial hemorrhages could be produced during the actual flow but rarely during the first half of the cycle.

Clinically, the increased frequency of hemorrhage at the menstrual period is recognized. There is also the well-known phenomenon of vicarious menstruation.

Kieser (1933) among many others, described hemorrhages from the nose, rectum, lung, and urinary bladder accompanying or replacing the uterine bleeding. Saitz (1935) observed small hematomas in the urinary bladder near the trigone on the first day of menstrual flow. Pottenger (1925) stated that hemorrhage from tuberculous foci was accompanied by an increased capillary permeability and hemorrhage.

Minot (1936) recorded three cases of intermittent menstrual purpura hemorrhagica with lymphocytosis and a decrease in the platelet count. David's cases (1926) of hemorrhagic diathesis at menstruation differed in that the platelets were not reduced. Ellman and Weber (1935) also described recurrent menstrual purpura. Other similar instances too numerous to mention have been recorded.

It is necessary also to mention menstrual edema. Thomas (1933) observed 2 patients who had edema only at the menstrual period. Molnár and Gruber (1934) described an edema of unknown origin occurring at the time of menstruation. Sweeney (1934) recorded the gain in weight and edema at menstrual time in a group of menstruating women. Atkinson and Ivy (1936) described a case of menstrual edema in which the edema appeared one week prior to the onset of menstruation. They also mention two other patients with premenstrual edema.

These phenomena of hemorrhage and edema that occur in the body in association with menstruation have been ascribed to various factors.

Seyderhelm and Heinemann (1930) believed the hemorrhages were the result of a lowering of the endothelial resistance which was determined by a lowering of the estrogen content of the blood. David (1926) concluded the changes were the result of ovarian dysfunction. Pistor (1935) stated that the endothelial system was influenced by ovarian hormones by way of alteration in the blood cholesterol. Pottenger (1925) held that a menstrual enzyme was responsible.

That the changes are incident to vascular spasm is suggested by many facts. 1. Similar changes in the skin capillaries as those observed during menstruation (increased capillary fragility) can be brought about by the production of vascular spasm in the skin vessels. This was demonstrated as follows. Eight human subjects were chosen, one female and seven males, and into each adrenalin was injected. Males were used in order that the menstrual rhythm would not interfere. Tests were made before injection to establish the normal negative pressures required to produce capillary hemorrhage for each individual.

To each individual then, 0.1 c.c. to 0.4 c.c. of 1:1000 adrenalin solution was injected subcutaneously following the method of injection suggested by Luckhart and Koppanyi (1926). These amounts of adrenalin produced in all the subjects a generalized blanching of the skin and a marked ischemia about the site of injection. Each promptly developed a tremor, nervousness, palpitation, and increased pulse rate.

In all the individuals so treated there was within twenty to forty-five minutes, while the general blanching was still evident, a definite, abrupt decrease in the negative pressure required to produce capillary hemorrhage (Chart 6). This decrease amounted to between 100 and 200 mm. of mercury. A return to normal occurred usually within two hours. The experiment was repeated three different times with identical

results. The pattern of reaction reduplicates that observed in the peripheral vascular system in normal women during the bleeding phase of the cycle (Chart 2, May 27).

2. The vasospasm produced by the adrenalin injections was associated with subjective clinical symptoms identical to those observed by the patients immediately before menstruation. In correlation with this is the fact that in many of the subjects (Subjects 10 and 18; Charts 3 and 4) subjective symptoms of impending menstruation developed simultaneously with the increase in capillary fragility, which I believe is the result of vasospasm.

3. Vasospasm of the skin vessels was observed directly by Hagen (1922). By the use of a capillary microscope he noted spasm in these vessels during the premenstrual period. During the time of active flow the spasm relaxed.

4. Eichbaum (1929) observed that epinephrine produced less increase in blood pressure during menstruation than at other times of the cycle and concluded this was due to the fact that the smooth muscle was already in spasm at this time.

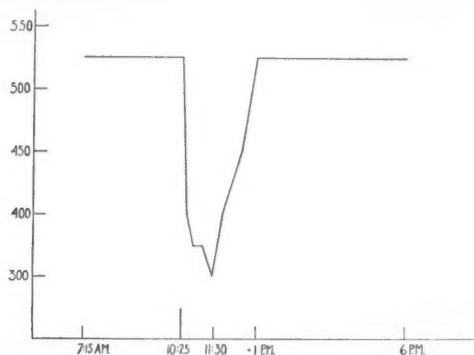


Chart 6.—This demonstrates increased capillary fragility following the subcutaneous injection of 0.2 c.c. of 1:1000 adrenalin solution. The increase in capillary fragility occurs at the time that spasm in the skin vessels is evidenced by blanching of the skin. The initial sudden increase came ten minutes after injection. The entire reaction duplicates that observed in the skin capillaries in association with menstruation.

5. Gebert (1936) noted a delay in the time of the dermographic reaction to skin irritation in the premenstrual phase of the cycle and ascribed it to the fact that the skin capillaries were in spasm. Petersen (1934) has described vascular spasm and states that the peripheral vasospasm occurs in association with the menstrual rhythm irrespective of meteorologic conditions.

6. DeLisi (1935) demonstrated by chemical tests that there was a premenstrual increase in the epinephrine content in the blood with an associated rise in blood pressure which is consistent with the occurrence of vascular spasm.

7. The changes noted in capillary fragility in this work and the altered capillary fragility and permeability noted by others can and do result from vascular spasm (Landis, 1937, Petersen, 1936, and others). Landis (1937) states that vascular spasm produces an anoxemia of the capillary endothelium. This reaction of spasm and anoxemia, he concludes, is reversible unless the anoxemia goes too far, in which case the

reaction then produces a nonreversible increase in permeability. It is conceivable that rupture of the capillaries with consequent hemorrhage might occur with relatively more ease upon resumption of circulation. Bartelmez (1933) has demonstrated this microscopically in the uterine endometrium at the onset of menstruation. Such phenomena of vasospasm with altered permeability at menstrual time might well explain the occurrence of menstrual edema.

8. Vasospasm occurs in the uterus simultaneously with the increase of capillary fragility demonstrated in the capillaries of the skin. In the uterus, particularly in the endometrium, a vascular rhythm has been demonstrated. It consists of rhythmic spasms of the terminal arteries and arterioles which coincide with the rhythmic changes observed in this paper in the peripheral vascular field.

Lahm (1926) described one uterus in which he noted vasoconstriction in the spiral arteries in the myometrium and deeper portions of the endometrium. Meyer-Ruëgg (1918-1919) noted a similar phenomenon. To Bartelmez (1933), Markee (1933), and Daron (1936) belongs the credit for conclusive establishment of the facts and the complete description of the details of vascular spasm in relation to menstruation. The spasms, as observed by Markee in *Macacus rhesus*, became evident about the nineteenth day of an ovulatory cycle. As the time of menstruation approached, the spasms occurred more frequently and each lasted for a longer time. Just before the onset of the flow some individual spasms persisted for twenty-four to forty-eight hours. Bartelmez (1933) has concluded that in the human being the spasms produced an ischemic necrosis of the capillary endothelium and the superficial endometrial tissues. Upon relaxation of the spasm the resumed circulation burst the capillary walls and a superficial subepithelial hematoma was formed. Markee (1933) observed this in ocular transplants. Subsequent desquamation of the superficial endometrial tissue occurred in the region of the particular vessel that evidenced prolonged spasm. Thus, these workers concluded that physiologic vasoconstriction was adequate to account for the tissue loss and the bleeding that characterizes any type of menstruation.

Extensive and profound vascular spasm in the uterus was described by Bartelmez (1933) and Markee (1933) to vary in its time of onset. The phenomenon occurred at times in its most profound state a day or two before menstruation and at other times only an hour or two before. Similar variations in the time of appearance of the marked increase in the fragility of the skin capillaries in the subjects of this experiment (Chart 2, May 27 and Chart 4, November 27) suggest a close relationship of the two phenomena.

9. Finally, the demonstrated generalized vasospasm with resulting anoxemia and ischemia may readily account for the various phenomena associated with menstruation. These phenomena occur only at menstruation, and it is only at this time that vascular spasm is evident. Some of these are: epileptic seizures only at menstruation, vicarious menstruation, hemorrhages in various tissues and organs at menstruation and late premenstrual stage, diarrhea occurring regularly at menstrual time, and menstrual edema. In some cases of hemorrhagic diathesis hemorrhage occurs at menstrual time in spite of the fact that no variations in the characteristic blood picture can be shown. The added factor of a generalized vasospasm and increased capillary permeability at menstruation, demonstrated in this paper, might well explain such a phenomenon.

Tangible evidence is offered in support of the suggestion that ischemia in the uterus may be a cause of dysmenorrhea. In Subject 10 (Chart 3,

August 13) an unusually prolonged period of vascular spasm in the skin capillaries was accompanied by severe dysmenorrhea and profuse menstruation, probably dependent upon coexisting spasms in the vessels in the uterus.

CONCLUSIONS

1. This study indicates that in the human female with normal ovulatory menstruation, there are rhythmic changes in the capillaries of the skin that are associated with the cyclic menstrual rhythm.
2. These rhythmic changes are essentially changes in capillary fragility.
3. During the few days prior to and on the first day of menstruation, capillary hemorrhage is produced with relatively greater ease than during the remainder of the cycle.
4. It is indicated that these rhythmic changes are the direct result of vascular spasm.
5. In functional uterine bleeding, the vascular rhythm in the skin capillaries is profoundly disturbed, and it is completely dissociated from the menstrual rhythm.
6. These facts indicate that menstruation which is evidenced as a local vascular phenomenon is in reality a part of a demonstrable generalized vascular phenomenon present in the entire body.

I would like to express my appreciation for technical assistance rendered by Barbara Phares.

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DISCUSSION

DR. CARL A. JOHNSON.—The importance of circulating substances as regulatory factors of the blood vessels has recently been brought forcibly to our attention. A few years ago there was great enthusiasm for the surgical relief of vasospastic conditions of the extremities through operations on the sympathetic nervous system. Reports of success were, however, short lived because of the recurrence of symptoms. The circulation apparently returned to the preoperative condition within a comparatively short time following these operations. Studies soon showed that sympathectomized blood vessels became sensitive to circulating substances in the blood, particularly epinephrine.

These investigations and those of Dr. Brewer stress the importance of the hormonal control of the blood vessels, not only with regard to vasoconstriction and vasodilatation, but also to hemorrhagic conditions. This study should mark only the beginning of investigations of the effects of other hormones upon the peripheral blood vessels.

DR. GEORGE BARTELMEZ.—This additional evidence (Dr. Brewer) that the phenomenon of menstruation involves general bodily changes is significant. The conclusion is that we are dealing with general changes in the body as a whole. The uterine vessels, however, are more sensitive than any others and they alone suffer extravasation, normally.

One of the most important of Dr. Brewer's findings is the demonstration of a fundamental difference between menstruation and functional bleeding. That this method may be used to differentiate between ovulatory and nonovulatory cycles is unlikely, because we have now enough evidence to state that there are transitions between the typical ovulatory cycle and cycles in which ovulation has not occurred. Such intermediate conditions may be associated with cystic follicles or with early regression of the corpus luteum.

DR. WALTER SCHILLER.—When physiologists began to investigate the cyclic functions of female genitalia, they placed menstruation in the foreground, considering it as the summit of the cyclic changes. In time this conception was changed, when it was realized that the purpose of the intermenstrual changes is not menstruation but pregnancy. The changes the female organism undergoes to adapt itself for gestation, start immediately after ovulation. Menstruation only signifies failure in establishing gestation and the cancellation of the preparations for this gestation. Founded on this interpretation, we have changed the term premenstrual changes, to the term pro gravid changes, expecting to find the maximum of pro gravid changes in the premenstrual phase.

In agreement with this, a great number of determinations carried out by physiologists proved that the maximum of changes concerning blood morphology, blood biochemistry, blood pressure, etc., can be found not during menstruation, but during the premenstrual phase. Keitler, by careful investigation of 60 cases of so-called vicarious menstruation, proved that the extrauterine bleeding takes place in the phase of premenstrual hyperemia, and in consequence of loss of blood the uterine bleeding is reduced.

Joseph Novak, of Vienna, confirmed that laparotomies in which the abdominal wall is hyperemic generally are carried out in the premenstrual phase, whereas the so-called "dry" laparotomies, in which there is very little hemorrhage during section of the abdominal walls, are performed in the postmenstrual phase. The most interesting findings of Dr. Brewer's work correspond to these findings and confirm the fact that the maximum of physiologic changes are found during the premenstrual phase.

DR. SAMUEL SOSKIN.—The previous discussers have already emphasized the fact that menstruation is not a process confined to the uterus, but is accompanied by general changes throughout the body. In this connection one might also mention the recent work of Rubenstein who has demonstrated rhythmic changes in the

body temperature and basal metabolism accompanying the menstrual cycle. Since there are so many general phenomena involved, it seems unwise to conclude without further evidence, that the particular change which the author has studied is the one responsible for the initiation of menstruation in the uterus.

It may be of interest to mention that Dr. Chassar Moir of London has postulated vascular spasm in the uterus as an explanation for the painful contractions of dysmenorrhea. This was based upon the fact that the arterial pulsations transmitted from a recording balloon inserted in the uterus, disappeared at the height of the uterine contractions. Drs. Lackner, Krohn, and myself had occasion to make similar observations in our studies on uterine motility in dysmenorrhea. We used a more sensitive recording system and found that even at the height of the severe uterine contractions of dysmenorrhea, the arterial pulsations persisted. This observation speaks against vascular spasm in the uterus, even under conditions where such spasm might be expected to be greater than normal.

My remarks are not intended to show that Dr. Brewer's interpretation of his results is wrong, but I think they do indicate that his conclusions are somewhat premature.

DR. BREWER (closing).—I, of course, knew there were many other phenomena associated with menstruation, but the paper was concerned only with the changes in the peripheral vascular system.

UNPREDICTABILITY OF THE PHENOMENA ACCOMPANYING THE MENSTRUAL CYCLE IN NORMAL WOMEN*

WITH SPECIAL REFERENCE TO THE TIME OF OVULATION

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SCIENTIFIC interest in the determination of the exact time of ovulation in the menstrual cycle has been somewhat overshadowed by the less critical, popular interest in the related Ogino-Knaus theory of the so-called "safe period." It may be accepted that the period of fertility during a menstrual cycle is restricted to a certain number of days preceding and following ovulation, depending upon the duration of viability of the sperm and the unfertilized ovum. The establishment of a "safe period" for a particular woman therefore depends upon the accuracy with which we can determine or predict the time of ovulation for her, and also upon the correctness of our assumptions as to the life-span of the free sperm and ova.

The time of ovulation in women has been approximated by a number of investigators in a variety of ways.¹⁻¹² But the most widely exploited method in normal women probably has been that of Knaus^{1, 2} based upon observations of the motility of the uterus and the reaction of this organ to the administration of extracts of the posterior lobe of the pituitary gland. According to Knaus, the uterus of the nor-

*Presented at a meeting of the Chicago Gynecological Society, March 18, 1938.

mal woman manifests spontaneous, rhythmic contractions during the first fourteen days of a twenty-eight to thirty-day menstrual cycle. During this portion of the cycle, which may be termed the follicular phase, the uterus responds with increased contractions to the administration of posterior pituitary extract. Ovulation occurs on the fifteenth day. Twenty-four hours later the uterus has become flaccid and quiescent, and no longer responds to posterior pituitary extract. This corpus luteum phase lasts from the sixteenth day of the cycle until forty-eight hours before the ensuing menstruation. At this time the uterus reverts to the motility and responsiveness characteristic of the first fourteen days of the cycle. If one can accept these findings of Knaus as correct, then one can believe with him that it is possible to determine the date of ovulation with some degree of exactitude, by observing the day of the cycle upon which the uterus ceases to respond to the administration of pituitrin. It would thus be possible to establish the "safe period" for healthy women with regular menstrual periods, providing the duration of viability of the sperm and ovum were known.

Unfortunately, a number of authors have been unable to confirm Knaus's results or to concur in his assumptions.

Klaften and Ruffel¹² found that in 11 cases out of 34 studied by Knaus's technique, their results were opposed to his. Similarly, Tachezy³ studied 20 patients, and found that only 20 out of 67 observations which he made conformed with those of Knaus. Schultze,¹¹ who used a somewhat different technique, has even gone so far as to conclude that the uterine reaction to posterior pituitary preparations is augmented in the second half of the menstrual cycle. Finally, Hermstein⁶ has emphasized the great possibilities of error in calculation of the "safe period," when one considers the uncertainty of our knowledge concerning the viability of the ovum and sperm under different conditions in different parts of the female genital tract. He also points out the variability in the length of the menstrual cycle in many perfectly healthy women at different times. A more complete account of these theoretical considerations will be found in recent review articles.¹³⁻¹⁶

Our interest in the above problem was aroused during our previous studies on the motility of the human uterus.^{17, 18} We had noted considerable variability in the motility, endometrium, blood and urine hormone content, and length of the menstrual cycle, in a few normal women used as controls for other patients. It seemed apparent that, if these normal women were at all representative, the component phenomena of the menstrual cycle were too irregular and unpredictable to form a basis for such calculations as those of Knaus. It therefore seemed worthwhile to study a larger series of normal women by the same methods, and also to observe the effects of the administration of posterior pituitary extract at various times in the menstrual cycle.

METHODS

This work was done on women between the ages of 19 and 42 years, in whom a careful history and a thorough gynecologic examination revealed no abnormality in sexual structure or function. Our object was to record the spontaneous uterine motility and the uterine response to the administration of posterior pituitary prep-

arations, to observe the state of the uterine endometrium, and to determine the urinary excretion of prolactin and estrin, as frequently as possible during the menstrual cycle of normal women. The particular difficulty of this work was to induce normal women to undergo repeatedly the necessary inconveniences and minor discomforts involved. There was also the important consideration that too frequent disturbance of the uterus, especially as regards endometrial biopsy, might interfere with the normality of our conditions. The procedure finally adopted represents a compromise between the theoretically desirable and the practically expedient.

We were able to make the above observations, once in each quarter of the menstrual cycle, in each of 15 normal women. However, the 4 sets of observations on each woman were not made during a single cycle. In most of the cases they extended over 2 cycles, the studies being made during the first and third quarters of one cycle, and during the second and fourth quarters of the next. In some cases, each of the 4 sets of observations was made during a quarter of 4 different cycles. For purposes of comparison, careful records were kept of the exact length of every cycle during which the subjects were studied.

Our experimental methods have been fully described in a previous publication.¹⁷ On the day of the experiment, a rubber balloon was inserted into the uterus with aseptic precautions. After a half hour rest period, to allow for recovery from the initial disturbance, if any, the kymograph record of uterine motility transmitted from the balloon was begun. Fifteen minutes later, 1 c.c. of obstetric pituitrin (Parke-Davis) was injected intramuscularly. A second injection of pituitrin, or an injection of pitocin or pitressin, was administered fifteen minutes after the first injection. The kymographic tracing was continued for at least half an hour after the last injection. A strip of uterine mucosa was removed by suction curette after each experiment. Eight of our subjects made twenty-four-hour urine collections on the days preceding their experimental days and ending on the morning of the latter. These specimens were assayed for prolactin and estrin content.

RESULTS

There would be little purpose in attempting to give all our results in detail here, because their rather considerable bulk renders them unwieldy and difficult to correlate. We have chosen, instead, to present brief summaries of those data which seem to yield significant correlations. Some examples and trends are graphically illustrated.

UTERINE MOTILITY, AND RESPONSE TO PITUITRIN

A total of 60 kymograph tracings of uterine motility was made in our 15 normal subjects; 30 records during the first half of the menstrual cycle, and 30 during the second half. Of the 30 tracings made during the first half of the cycle, only 8 showed definite spontaneous uterine motility. There was no instance of spontaneous motility in the second half of the cycle, except for 3 tracings made within forty-eight hours of the onset of the next menstrual period. Thus while the trend of these results follows the pattern described by Knaus, the large number of quiescent uteri during the first half of the cycle makes it impossible to use the presence or absence of spontaneous uterine motility as a criterion of time in the menstrual cycle. Incidentally, however, the fact that 49 out of the total number of 60 records showed no uterine contractions after insertion of the balloon, answers Dickinson's (discussion¹⁴) criticism of the balloon method. It does not seem likely when uterine contractions are found that they are merely the result of the presence of a foreign body in the uterus.

The intramuscular injection of 1 c.c. of pituitrin caused increased uterine motility in only 23 of the 30 trials during the first half of the cycle, and in 8 of these cases the reaction was very slight. Of the 22 tests made before the last two days of the second half of the cycle, all of which should have been negative according to Knaus, only 12 were negative while 10 showed a definite response to pituitrin. The 8 tests

made within forty-eight hours of the next menstrual period, all of which should have been positive according to Knaus, yielded only 5 positive responses while 3 showed no response to pituitrin. The failure in response of any of the above cases can hardly be ascribed to an inadequate dosage of pituitrin, since in no case was a response elicited by the second injection of pituitrin if it had failed to appear after the first dose.

It is apparent, from the above, that the Knaus method of determining the time of ovulation from the uterine response to posterior pituitary extract, is unreliable to say the least. The results of such tests in different, apparently normal women, are unpredictable. Illustrative examples are given in Figs. 1 to 4. Two cases which yielded results like those of Knaus are shown in Figs. 1 and 2. Fig. 3 is from an equally normal woman, who gave completely opposite results. Fig. 4 is a composite of results from 5 different women, showing that the normal uterus may exhibit an increased motility after the injection of pituitrin, in any part of the menstrual cycle. It is noteworthy, however, that the 3 women who yielded the previously

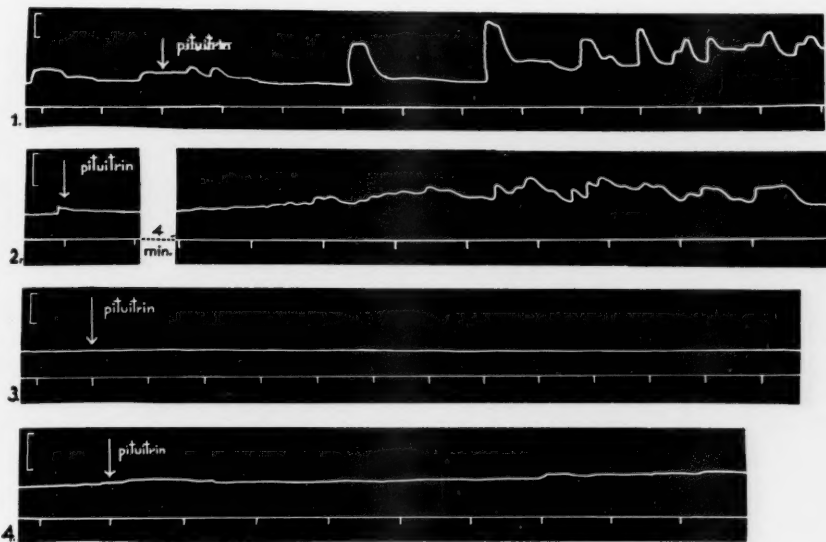


Fig. 1.—Mrs. B. H., aged 42 years. A "Knaus-positive" case. Showing representative portions of records taken at 4 different times during the menstrual cycle.

Record 1: 3rd day of a 24-day cycle
Record 2: 6th day of a 25-day cycle
Record 3: 19th day of a 24-day cycle
Record 4: 21st day of a 24-day cycle

The vertical ticks on the base line represent time intervals of one minute. The calibration mark in the upper left hand corner of each record indicates the movement of the recording lever, equivalent to a uterine contraction which would decrease the intrauterine volume by 1 c.c. The gap in the second record represents a 4-minute period excised from the record, in order to allow more complete presentation of the more significant portion which follows. The straight-line tracing shown in Record 3, means that no uterine contractions whatever were observed throughout the whole of that experimental observation, lasting at least one hour.

cited 11 instances of spontaneous uterine motility before the administration of pituitrin, all fell into the "Knaus-positive" group. It may well be that Knaus's findings might be confirmed in a selected group of women with particularly active and responsive uteri. But, his results are not obtained in most, apparently normal, women.

UTERINE RESPONSE TO PITOCIN AND PITRESSIN

Some results obtained from a comparison of the effectiveness of pitocin and pitressin (Parke-Davis) with that of pituitrin, in causing increased motility of the

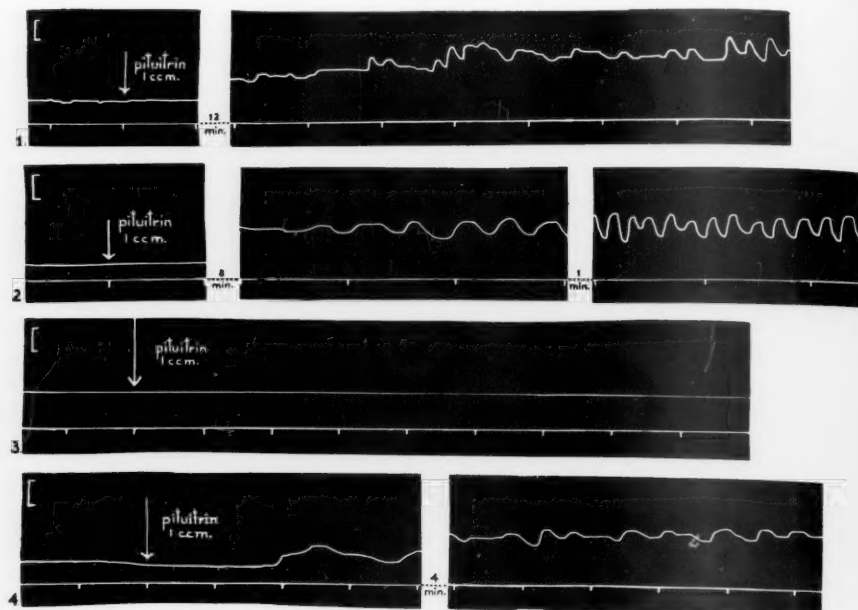


Fig. 2.—Mrs. L. K., aged 29 years. A "Knaus-positive" case.

Record 1: 8th day of a 20-day cycle

Record 2: 10th day of a 22-day cycle

Record 3: 15th day of a 22-day cycle

Record 4: 20th day of a 21-day cycle

Conventions as for Fig. 1.

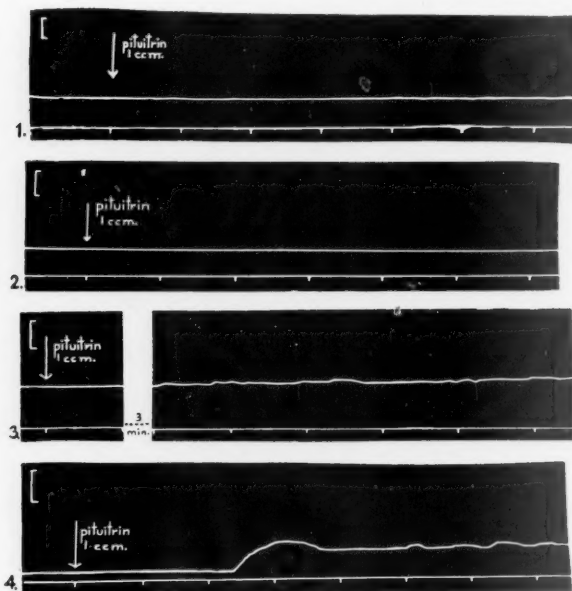


Fig. 3.—Mrs. A. K., aged 39 years. A "Knaus-negative" case.

Record 1: 2nd day of a 29-day cycle

Record 2: 8th day of a 30-day cycle

Record 3: 15th day of a 30-day cycle

Record 4: 22nd day of a 30-day cycle

Conventions as for Fig. 1.

uterus, may be of interest. This comparison arose from our original intention to use pitocin as the logical oxytocic agent for the above studies. However, this idea was abandoned when we found that in some cases in which pitocin had no effect on uterine motility, an injection of pituitrin given fifteen minutes later did cause increased contractions. This never occurred when the primary injection was either pituitrin or pitressin.

Thirty-seven tests of pitocin were made (as described for pituitrin) in our 15 normal subjects, using 1 c.e. (10 international units) intramuscularly in place of the first injection of pituitrin. Of the 16 injections given during the first half of the cycle, 7 resulted in increased uterine motility while 9 did not. Of the 14 tests made before the last two days of the second half of the cycle, 2 showed increased contractions while 12 did not. Of the 7 trials during the forty-eight hours preceding the next menstrual cycle, 3 yielded increased motility while 4 did not.

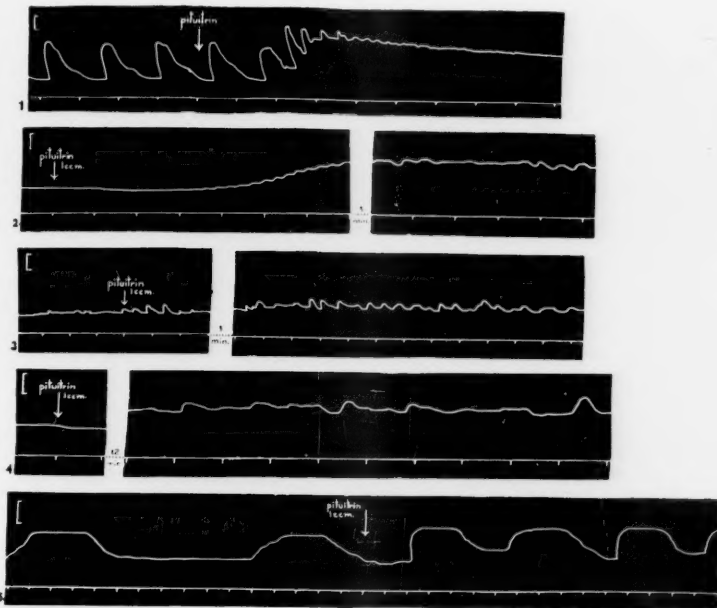


Fig. 4.—Composite of results from 5 different women, showing increased uterine motility after pituitrin administration at various times in the menstrual cycle.

Record 1: Mrs. S. A., aged 34 years; 4th day of a 26-day cycle
 Record 2: Mrs. S. S., aged 28 years; 13th day of a 34-day cycle
 Record 3: Mrs. V. W., aged 28 years; 16th day of a 29-day cycle
 Record 4: Mrs. K. K., aged 42 years; 26th day of a 30-day cycle
 Record 5: Mrs. E. S., aged 25 years; 24th day of a 26-day cycle
 Conventions as for Fig. 1.

The severe systemic reaction, including abdominal cramps and tingling at the fingertips, which followed the injection of 1 c.e. (20 units) of pitressin, limited the number of cases in which it could be tried. Ten records were obtained from 8 of our subjects. Of the 5 tests made during the first half of the cycle, 3 resulted in increased uterine motility while 2 did not. Pitressin had no effect in the 5 trials made during the second half of the cycle.

Table I summarizes and compares the relative effectiveness of pituitrin, pitressin, and pitocin, in causing increased uterine motility during the different stages of the menstrual cycle. It may be seen that none of these preparations act in the manner described by Knaus. Strangely enough, it is the blood pressure-raising principle, rather than the oxytocic, which most nearly approaches his results. However, our data on pitressin are insufficient to warrant definite conclusions.

TABLE I. RELATIVE EFFECTIVENESS OF PITUITRIN, PITOCIN AND PITRESSIN IN CAUSING INCREASED UTERINE MOTILITY AT DIFFERENT STAGES OF THE MENSTRUAL CYCLE*

| | FIRST HALF OF THE CYCLE | SECOND HALF OF THE CYCLE | LAST 2 DAYS OF THE CYCLE |
|----------------------------|----------------------------|-----------------------------|-----------------------------|
| Pituitrin | $\frac{23}{30}$ 77% | $\frac{10}{22}$ 45% | $\frac{5}{8}$ 62% |
| Pitocin | $\frac{7}{16}$ 44% | $\frac{2}{14}$ 14% | $\frac{3}{7}$ 43% |
| Pitressin | $\frac{3}{5}$ 60% | $\frac{0}{5}$ 0% | — |
| Results according to Knaus | 100% | 0 | 100% |

*The fractions in the upper left hand corner of the compartments in this table give the actual figures from which the percentages were calculated. The numerator represents the number of instances in which the administration of a particular posterior pituitary preparation was followed by increased uterine motility. The denominator represents the total number of tests made with that preparation, under the specified conditions.

UTERINE ENDOMETRIUM

Fig. 5 graphically presents the results of the histologic examination of 60 endometrial biopsies, taken once in each quarter of the menstrual cycle, in each of our 15 normal women. Because of the varying length of the cycle in different women, and at different times in the same woman, the proportionate rather than the absolute time in the cycle has been plotted. This makes our data comparable as to time, and enables one to judge the tendency of the results in the group as a whole, from the distribution of all the plotted values. The 4 observations on each subject are identically numbered, so that the course of events in each may be followed through the cycle. It may be seen that the group of women as a whole shows the development of endometrial change through the cycle, in the generally accepted manner. But there are enough individual deviations from the general pattern to make the latter an unreliable criterion of normality in any given woman. It is evident at a glance, for example, that 4 out of the 15 normal women (or over 25 per cent) failed to show a secretory endometrium during the last quarter of the menstrual cycle.

It might be supposed that those cases which failed to show a secretory endometrium during the second half of the menstrual cycle, were the same individuals who did not respond to pituitrin in the manner described by Knaus. If this were so, both these phenomena could be ascribed to the occurrence of anovulatory cycles in these women. Correlation of these data, however, reveals the fact that the 10 instances of positive motility response to pituitrin in the second half of the cycle (excluding the last forty-eight hours) occurred in conjunction with 1 negative, 4 proliferative, and 5 secretory specimens of endometrium. The 12 instances in which there was no response to pituitrin, on the other hand, were accompanied by 6 proliferative and 6 secretory specimens of endometrium. This equal division of the incidence of both the secretory and the nonsecretory endometrium between the "Knaus-positive" and "Knaus-negative" cases, forces the conclusion that our results cannot be explained by the supposed occurrence of anovulatory cycles.

URINARY EXCRETION OF PROLAN AND ESTRIN

The twenty-four-hour urinary excretions of prolan and estrin, in 8 of our subjects, are plotted in Figs. 6 and 7, respectively. The plotted times are proportionate, and the 4 determinations done for each woman are identically numbered, as described for Fig. 5. We are well aware of the fallacy, emphasized by Frank,¹⁰ of judging the hormone excretion of an individual from isolated twenty-four-hour urine specimens during the menstrual cycle. Therefore, we shall not attempt to

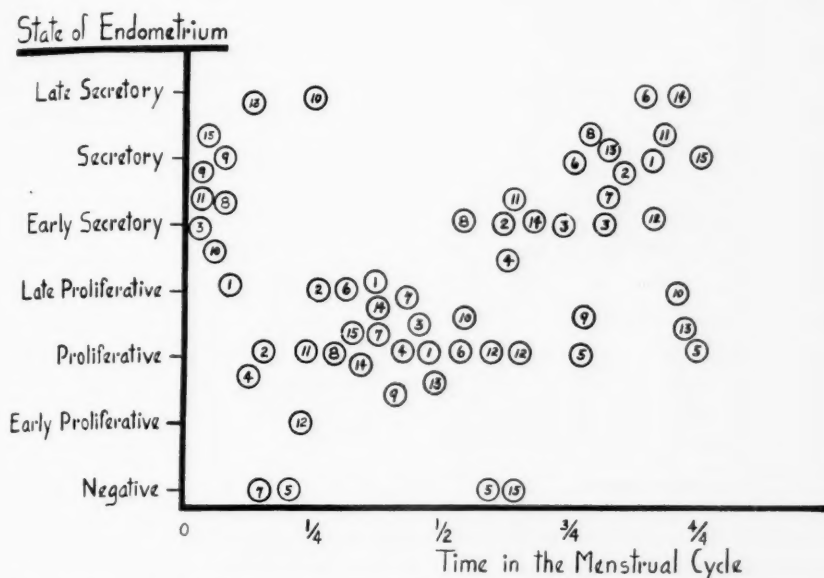


Fig. 5.—Histologic state of uterine endometrium, observed once in each quarter of the menstrual cycle, in each of 15 normal women. The 4 observations on each woman are identically numbered. The time of each observation is plotted as a proportion of the length of the menstrual cycle in which it was made. All the results are therefore comparable as to time. Zero time represents the day of onset of the menstrual flow.

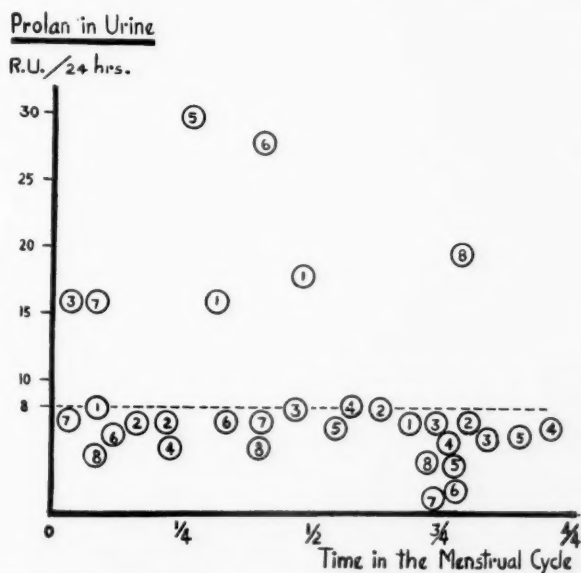


Fig. 6.—Quantitative daily prolan excretion observed once in each quarter of the menstrual cycle, in each of 8 normal women. Since the minimum range of our prolan assay was 8 rat units, the position of the plotted points below the horizontal broken line does not have any quantitative significance other than "less than 8 rat units per twenty-four hours." Other conventions as for Fig. 5.

draw any conclusions from the variations in excretion of any single one of our cases. But since our method of presentation of these data tends to compensate for individual peculiarities, the general trend of our results as a whole should be a good index of the normal pattern of hormone excretion. According to the results of Kurzrok, and others,¹⁹ and Frank,¹⁰ we should expect to find a grouping of high values for prolan excretion at or about the middle of the cycle (Fig. 6). According to the same authors, we should also expect to see certain peaks in the values for estrin excretion about the middle and toward the end of the cycle (Fig. 7). However, neither of these tendencies is clearly visible in our graphs. It must be concluded that, even though certain normal women display the characteristic cyclic variations in hormone excretions described by some authors, many normal women do not follow the same pattern. These results should make one reluctant to infer the presence of a hormonal abnormality from urinary assays, unless the values obtained are significantly above or below the entire range of values ordinarily found in normal women during the menstrual cycle.

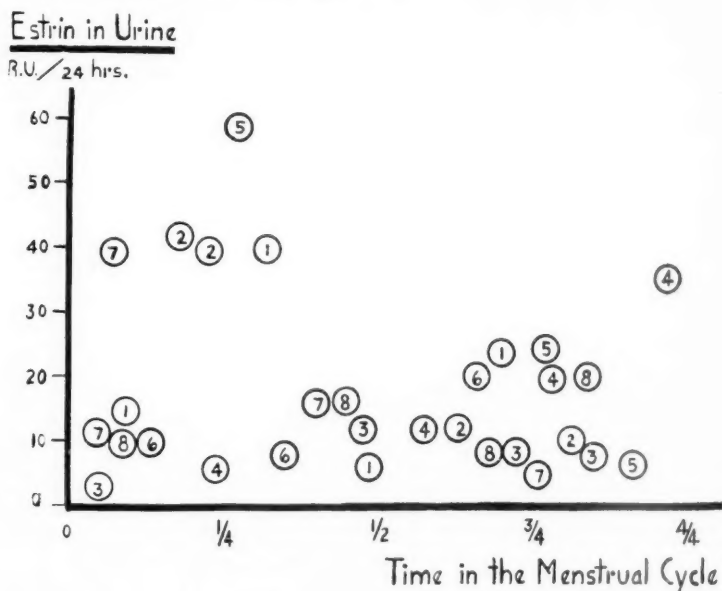


Fig. 7.—Quantitative daily estrin excretion observed once in each quarter of the menstrual cycle, in each of 8 normal women. Conventions as for Fig. 5.

SUMMARY AND CONCLUSIONS

A number of the important aspects of the menstrual cycle have been studied, throughout the cycle, in 15 normal women. The phenomena observed included the spontaneous motility of the uterus, uterine response to the administration of preparations of the posterior pituitary gland, changes in the uterine endometrium, and the urinary excretion of prolan and estrin.

The outstanding observation made during this work has been the irregularity of the above phenomena in various normal women, and their unpredictability for any given normal woman. In other words, while the above phenomena tended to follow certain behavior patterns, the number of exceptions was so great as to preclude the use of these phenomena as reliable criteria of normal sex function.

The results obtained from the administration of posterior pituitary preparations do not agree with those of Knaus from which he concluded that there was a single regular ovulation time for normal women. Either his test is highly unreliable, or normal women (in this country at least) ovulate at widely differing times in the menstrual cycle. In either case grave doubt is cast upon the Ogino-Knaus theory of the so-called "safe period."

A comparison of the relative effectiveness of pituitrin, pitocin, and pitressin in causing increased uterine motility, showed that the supposedly pure oxytocic principle was less effective than the mixture composing obstetric pituitrin. Pitressin has potent oxytocic properties, *in vivo*.

As regards the urinary prolactin and estrin, since no regular pattern of excretion during the menstrual cycle was found, it is concluded that extreme caution should be exercised in the interpretation of such assays, unless the amount of hormone excreted is significantly above or below the entire range of values found during the menstrual cycle of normal women.

We are greatly indebted to Dr. S. Charles Freed for his cooperation in assaying our many samples of urine for prolactin and estrin content, and to Dr. Otto Saphir for his interpretation of our histologic preparations.

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DISCUSSION

DR. M. EDWARD DAVIS.—Dr. Lackner and his associates presented the results of their experiments on the Ogino-Knaus concept for determining the time of ovulation. Their results add additional proof to many previous experiments which disagree with this concept. It is unlikely that variations in uterine motility occurring at various periods during the normal menstrual cycle can be regarded as solely due to endocrine factors. Other factors must necessarily influence these changes. Smooth muscle normally contracts spontaneously. Furthermore, the intact uterus has both an intrinsic and extrinsic innervation.

The Ogino-Knaus experiments have been confirmed largely on laboratory animals, particularly the rabbit. One must remember that ovulation in the rabbit does not occur periodically of its own accord, but follows copulation or mechanical stimulation of the reproductive tract. In women ovulation occurs periodically as part of the normal cyclical changes. The mechanism for the production of ovulation in women

must be somewhat different than in the case of nonspontaneously ovulating animals. These species variations must be considered in the interpretation of experimental procedures and results.

Allen, Burr and Musselman, and other workers have provided us with a new method for determining the time of ovulation. Their potentiometer which records minute changes in electrical potentials occurring in tissues may provide us with an instrument for accurately recording the time of ovulation. This method is still too complicated for clinical use, but it offers considerable possibility for future work.

Dr. Adair and I have been interested in the study of uterine motility for many years. In 1935 we reported the results obtained in the use of various oxytocic agents. We found that the two fractions of the posterior pituitary exhibited marked oxytocic activity when given to women in the immediate post-partum period by the intravenous route. Pitressin and pitocin exhibited almost equal oxytocic activity.

DR. EUGENE M. K. GEILING.—The hormones from the posterior portion of the hypophysis are among the most powerful ones in the body. One of the reasons we have not been able to isolate them is because of the extreme difficulty of getting sufficient material to work with. One begins to wonder, however, what is the function of these posterior lobe principles. In a series of hypophysectomized animals, it was recently found that the animals ovulated quite normally.

It is very dangerous to compare results in animals with those on human beings. We may have to start from the beginning in this matter of ovulation and make deductions from experiments conducted on the normal human being alone.

DR. LACKNER (closing).—This work was done on normal women in contradistinction to the work on the postnatal cases, and not on pregnant women, so perhaps the effect on the pregnant uterus is different from that on the nonpregnant uterus. I have just a few figures I would like to mention. We were somewhat astounded by the effect of pitressin. In 37 cases, 12 reacted to pitressin and 25 did not. However, in these same 37 cases in which we used pitressin, 31 reacted to pituitrin. There is, therefore, a decided difference between the effect of pitressin and pituitrin, which is manifested as a more pronounced reaction with pituitrin.

Rodecurt, Von M.: Examination of Smears of Operative Cases for Trichomonads,
Ztschr. f. Geburtsh. u. Gynäk. 115: 99, 1937.

Rodecurt believes that the ascension of trichomonas may be responsible for many of the pelvic infections and adhesions of unknown origin. The organisms can be found in cultures of pus from the tubes as well as adnexal tumors. Wagner and Hess have found the organisms in ascitic fluid, in placental tissue of abortions, in the walls of ovarian cysts, as well as in an abscess of the abdominal wall one week after the removal of an ovarian cyst. Rodecurt believes that stained smears are satisfactory if enough smears are examined before considering a result negative. He secured positive smears from curettings, fibromyomas, ovarian cysts, pus tubes, tubal pregnancies, in the appendix, and in normal placentas, but was unable to recover the organism from the blood stream or the nasal secretions. On the other hand, Wagner and Hess were able to culture trichomonads from the blood stream in 55 instances. The author believes that the *Trichomonas vaginalis* has a facultative pathogenicity and does not necessarily cause acute symptoms. When the organism is the only one found in specimens, it could be assumed to be the cause of the infection. Thus the author concludes: that the trichomonas may cause malignant degeneration in an originally benign tumor, that it may be the source of post-partum infections as well as peritoneal adhesions, that it may be responsible for many cases of tubal pregnancy if the tubes have been damaged by the organism, and that also unexplained abortions may be due to infection with this organism.

EUGENE S. AUER.

THE GEOGRAPHIC DISTRIBUTION AND EFFECT OF CLIMATE ON ECLAMPSIA, TOXEMIA OF PREGNANCY, HYPEREMESIS GRAVIDARUM, AND ABRUPTIO PLACENTAE

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THESE diseases occur only in the pregnant woman and the incidence for them should be approximately the same irrespective of race, climate, diet, or habits if they are caused by the pregnancy per se. However, if the occurrence varies in different countries, then the pregnancy is just one factor and if the other factors can be determined, studies may then be made to eliminate them and thus prevent the occurrence of these diseases.

Various authors of textbooks, in discussing the etiology of eclampsia, have stated that the disease is uncommon or rare in the tropics. The majority of them have ascribed the low incidence to the diet which they assumed to be mainly carbohydrate. So far as we know, they have cited no authorities or statistics for their statements.

Dass, in 1895, published an excellent review of eclampsia. He stated that Smellie, Lever, Simpson, and many other obstetricians had noted some periodicity in the occurrence of the disease, but no one had an explanation for it. Spiegelberg suggested that the quasi-epidemic occurrence of eclampsia might be brought about by "atmospheric influences, specially affecting the skin, an organ whose relations to fetal activity are, of course, well known." Dass thought that the high incidence of 0.94 per cent might be due to the sudden alterations in temperature and humidity which occur so frequently in Calcutta. His data also seemed to indicate that early childbearing was a distinct predisposing cause.

Because of the varied incidences of eclampsia Theobald believes that it cannot be caused by a placental toxin or by any functional or organic lesions in the kidneys. He states that from the known facts about eclampsia, together with his own experimental data, one is justified in stating that the disease is caused by toxins absorbed from the intestinal canal which, owing to a breakdown in the defenses of the body, are not detoxicated. He suggests that a deficiency of ionized calcium in the blood is the cause of the breakdown of the defenses of the body.

Buck noted that 320 cases of eclampsia out of 340 occurred during changeable weather.

Sachweh noted that the majority of 118 cases of eclampsia occurred in moist and especially moist and warm weather.

Von Heuss, in his series of 1,700 cases of eclampsia, noted that the attacks were especially started by summer thunderstorms and the "cold waves" which accompanied these.

Croom noted in Edinburgh that the incidence of eclampsia was highest in very cold, rainy weather, during which the relative humidity was very high. The incidence of eclampsia is greater in England and Ireland than it is on the continent of Europe.

Küstner stated that the highest incidence of eclampsia was in the spring and late summer and suggested that the ultraviolet radiation might be a factor.

Merletti and Grappa stated that a correlation existed between the incidence of eclampsia, changes in barometric pressure and humidity.

Kosmak reported some work of Harrar's which indicated that over a ten-year period the number of cases of eclampsia in the Lying-in Hospital in New York was greatest in March, April and May. The weather in these months is cold, damp and unsettled.

Hauch and Lehmann have made a thorough study of eclampsia in Denmark and have been able to account almost entirely for some of the peculiarities about its occurrence. Since their data are so complete and have been so carefully analyzed we include them to demonstrate how more than one factor may explain an alteration in the incidence of eclampsia and how carefully statistics must be interpreted. The decreased occurrence of eclampsia during the war in Germany and also in Denmark has been attributed to the lack of protein and fat in the diet and the increased work of the women, resulting in better oxidation of the food. However, these authors noted that the drop in the frequency began in 1915 before there was any lack of food and the great rise in incidence began at once in 1919 and reached its first maximum in 1921, when the condition of nutrition, as far as the majority of the population was concerned, had not changed materially. They attributed these changes to the marriage rate in nulliparae. The curve for the incidence of eclampsia and percentage of primiparae parallel each other. They believed that a change of income rather than food or mode of living was the predominant factor. During the war the income was low and therefore the number of marriages, which are chiefly of nulliparae and, therefore, if pregnancy occurs, more likely to have eclampsia, was decreased. After the war, the number of marriages increased and the incidence of eclampsia rose.

Hauch and Lehmann have also noted that there are more cases of eclampsia in March and August, and they attribute this to the fact that most marriages in Denmark occur in May and November, thus producing a 9- to 10-month interval. They also find that the incidence of eclampsia in Copenhagen is 0.31 per cent, in provincial towns 0.18 per cent, and in rural districts 0.10 per cent. They attribute this difference in part at least to a difference in the fertility of the women in the different locations. The annual number of births per 100 women between 16 and 49 years was thus: in the capital 10.4, in the provincial towns 14.2, and in the rural districts 17.5, despite a greater frequency of marriages in the towns. The annual number of marriages per 10,000 inhabitants was: in the capital 100, in the towns 83, and in the country 69. Fertility also decreases at a higher rate with increasing age within the urban population. Therefore, it can be assumed that there is a relatively greater number of primiparae, and thus younger women, among the childbearing women of the cities, thus accounting for the increased incidence of urban eclampsia.

Scheyer reviewed the incidence of eclampsia in Canton, China, and found that the largest number of cases occurred in September, December, January, and May, and the greatest number of patients with preeclampsia were found in July, August, and September. He attempted to correlate his findings with the meteorologic conditions but found it very difficult to do so.

Tottenham has studied the seasonal incidence of eclampsia in Hong Kong and noted that 66 out of 97 cases of eclampsia occurred during the months of September to February, inclusive. During this period the humidity is always below 80 per cent

whereas in the remainder of the year it is over 80 per cent. During this same period the temperature is at its minimum. Because of the small series he was unable to draw any definite conclusions.

Titus attributed the low incidence of eclampsia among the Eskimo to the fact that the temperature of their country is always low and constant. Thus, despite a high protein and fat diet, which presumably is a factor in causing eclampsia, these people are not subjected to sudden changes in the weather.

Harding and Drew stated that eclampsia is most frequent in Toronto, Canada, from November on, reaching a peak in March.

For several years we kept a record of the daily temperature, barometric pressure and humidity but the number of cases of eclampsia in our hospital was too small to enable us to draw any conclusions. However, we have repeatedly seen eclampsia occur when an abrupt change in the weather took place. The change might be from hot to cold or vice versa. We have also noted in the Toxemia Clinic that toxemic patients whom we have been following from week to week usually have their symptoms intensified when one of these abrupt changes occurs. If one could have available the records of all toxemic patients for a city of several million people together with the meteorologic data, we believe a very definite correlation would be found for the occurrence of eclampsia and abrupt alterations in the weather. These changes in the weather are certainly not the cause of the eclampsia but in susceptible patients these sudden alterations may cause disturbances in the water balance, acid-base equilibrium, and vascular system which result in intensifying the hypertension, edema, oliguria, etc., until convulsions and coma occur. Smith has reported that there is a water retention in the bodies of dogs and rats when the barometric pressure is lowered from 3 to 10 cm. of mercury during a period of from 12 to 48 hours. This disturbance of water balance is accompanied by restlessness.

We have collected data as to the occurrence of eclampsia, nonconvulsive toxemia, hyperemesis gravidarum and abruptio placentae from various parts of the world. Cases of abruptio were included because in a high percentage of the cases hypertension is also present. Hyperemesis was included because although it is not a toxemia yet it is a condition peculiar to pregnancy. Some of the material was obtained by a page-to-page study of all of the foreign journals at the American Medical Association Library for at least a 5-year period. Hospital reports were collected. One hundred and twenty questionnaires were sent to foreign hospitals and missionary doctors and 80 to hospitals in the United States. With but few exceptions everyone returned the form, either with their data or a note as to why they could not supply them. We asked for a 5-year summary, showing the annual number of deliveries, the number of patients with eclampsia, toxemia, hyperemesis, and abruptio, and the total and group maternal mortality. We realize that the hospital incidence of a disease is greater than for the

country as a whole, but in many of the foreign cities, only hospital statistics are available. We are also cognizant of the fact that the number of hospital deliveries in foreign countries is proportionately small as compared to all the deliveries, in contrast to the large cities in the United States where hospital deliveries form the major part. Furthermore, in India, China, etc., only patients with difficult complications are admitted to the hospital.

The meteorologic data have also been obtained for the various cities. The daily mean, maximum and minimum, temperature and inches of rainfall can be obtained for all cities in the United States but, as a rule, only the annual figures are available for foreign cities, especially those in Asia, Africa, and the islands.

The data for Europe and the British Isles are listed in Table I. The incidences for the latter are all from hospitals in London, Manchester, Dublin and Glasgow. Not only do these diseases occur more frequently here but the mortality due to them is much greater than that of any other country. We have no explanation for this, but believe it should be investigated further.

TABLE I. OCCURRENCE OF ECLAMPSIA IN EUROPE

| PLACE | MATERNAL MORTALITY % | ECLAMPSIA INCID. % | NONCONVUL- SIVE TOXEMIA INCID. % | HYPER- EMESIS GRAVIDARUM INCID. % | ABRUPTIO PLACENTAE INCID. % |
|----------|----------------------------|--------------------------|--|---|--------------------------------------|
| England | 1.94 | 1.61 | 8.02 | 2.24 | 2.79 |
| Scotland | 1.47 | 1.63 | - | 2.11 | 2.42 |
| Ireland | 0.58 | 0.61 | 16.60 | 0.55 | 0.84 |
| Germany | | 0.39 | 4.40 | 1.00 | 0.94 |
| France | | 0.58 | | | |
| Sweden | | 0.38 | | | |
| Finland | | 1.20 | | | |
| Denmark | | 0.86 | | | |

The incidence of these various diseases for the native population in other countries is listed in Table II. If data from several hospitals in the same city or from nearby towns were obtained, they were grouped and an average calculated.

Data were collected from 40 cities in the United States but only representative figures from various parts of the country are listed in Table III. The marked variation in the occurrence and mortality of these diseases, under supposedly ideal conditions, is noteworthy. What is the cause of the difference in mortality for eclampsia and toxemia? Are these diseases more severe in the South than in the North? Do the patients have less resistance? Is prenatal care more intelligently administered? Or is the method of treatment better in some cities? Similar questions are pertinent for hyperemesis gravidarum and abruptio placentae. More data must be collected before these questions can be answered.

Table IV lists the means for the incidence of eclampsia, etc., in the various countries. These figures are based on the data collected. The incidence of eclampsia for the world, based on our figures, is 1.0 per cent. The difference in the occurrence of these diseases of pregnancy between the British Isles and the United States is striking, and questions similar to those in the preceding paragraph are pertinent.

TABLE II. OCCURRENCE OF ECLAMPSIA IN THE NATIVES OF VARIOUS COUNTRIES

| PLACE | MATERNAL MORTALITY % | ECLAMPSIA INCID. % | NONCON- VULSIVE TOXEMIA INCID. % | HYPER- EMESIS GRAVI- DARUM INCID. % | ABRUPTIO PLACENTAE INCID. % |
|---------------------------|----------------------------|--------------------------|--|--|--------------------------------------|
| Algiers, Africa | --- | 2.85 | -- | 0.04 | -- |
| Cape Town, Africa | --- | 1.44 | -- | 0 | 1.60 |
| Tanganyika (etc.), Africa | 3.80 | 0.10 | 0.13 | 0 | 0.03 |
| Zulu, Africa | --- | Very rare | Rare | 0 | 0 |
| Ethiopia | --- | 0 | Rare | Rare | 0 |
| Belgian Congo, Africa | --- | 0 | -- | Rare | -- |
| Colombo, Ceylon | 3.90 | 2.76 | 2.93 | 0.21 | 1.40 |
| Porto Rico | --- | 2.54 | 27.33 | 0.25 | 0.33 |
| Shanghai, China | 1.97 | 1.27 | 3.31 | 0.22 | 0.83 |
| Hong Kong, China | 0.40 | 0.92 | 0.42 | 0.0001 | 0.31 |
| Virgin Islands | 0.39 | 1.25 | 0.26 | 0.26 | 0.46 |
| Japan | --- | 1.16 | -- | -- | -- |
| Philippine Islands | 2.62 | 1.03 | 0.16 | 0.27 | 0.18 |
| Bangkok, Siam | 2.21 | 0.68 | 2.87 | 0.59 | 0.23 |
| Fiji Islands | --- | 0.63 | -- | -- | -- |
| Trinidad | --- | 0.23 | 19.00 | -- | -- |
| New Zealand | --- | 0.20 | 2.09 | -- | 0.57 |
| Persia | 2.60 | 0.19 | 0.46 | Rare | 0.19 |
| Java | --- | 0.18 | -- | -- | -- |
| Hawaii | --- | 0.15 | 5.00 | -- | -- |
| British Malaya | 0.65 | 0.04 | 0.05 | -- | 0.05 |
| Alaska | --- | 0 | 0 | -- | -- |
| Australia | --- | 0 | 0 | 0 | 0 |

*--, No data given. 0, No cases.

TABLE III. OCCURRENCE OF ECLAMPSIA IN THE UNITED STATES

| PLACE | ECLAMPSIA | | NON- CONVULSIVE TOXEMIA | | HYPER- EMESIS GRAVIDARUM | | ABRUPTIO PLA- CENTAE | NUMBER OF DELIVERIES |
|-----------------------------|-----------|------------|-------------------------------|------------|--------------------------------|------------|----------------------------|-------------------------|
| | INC. % | MORT. % | INC. % | MORT. % | INC. % | MORT. % | INC. % | |
| Charlotte, N. C. | 7.2 | 5.6 | 29.40 | --- | --- | --- | --- | 500 |
| Charlottesville, Va. | 2.25 | 17.3 | 9.94 | 3.5 | 3.03 | 1.4 | 1.43 | 2,314 |
| Charleston, S. C. | 2.23 | 14.0 | 4.87 | 10.0 | 0.66 | 10.5 | 0.10 | 2,873 |
| New Orleans, La. (White) | 1.62 | 25.5 | --- | --- | 2.89 | 2.3 | --- | 2,903 |
| New Orleans, La. (Negro) | 0.71 | 30.7 | --- | --- | 1.24 | 5.9 | --- | 5,456 |
| Los Angeles, Calif. | 1.12 | 14.5 | 5.40 | 3.3 | 2.12 | 1.9 | 1.27 | 9,865 |
| Atlanta, Ga. (Negro) | 0.92 | 6.9 | 8.50 | 0.2 | 0.18 | --- | 0.72 | 7,799 |
| Texas | 0.50 | 19.0 | 1.45 | 2.9 | 0.21 | 6.7 | --- | 9,310 |
| Johns Hopkins | 0.80 | 6.8 | 23.30 | 0.9 | 0.11 | --- | 0.49 | 5,519 |
| Pittsburgh, Pa. | 0.59 | 21.8 | 1.58 | 10.4 | 1.35 | 5.2 | --- | 25,300 |
| Detroit, Mich. | 0.56 | 5.9 | 3.40 | 2.6 | 0.04 | --- | 0.87 | 9,118 |
| Jersey City, N. J. | 0.49 | 8.7 | 6.96 | 0.6 | 0.20 | --- | 0.46 | 9,438 |
| St. Louis Maternity | 0.42 | 17.0 | 3.35 | 0.4 | 1.15 | --- | 0.08 | 7,689 |
| Milwaukee, Wis. | 0.41 | 4.2 | 1.02 | 1.0 | 0.85 | 4.1 | 0.48 | 5,781 |
| Philadelphia, Pa. | 0.40 | 10.0 | 0.19 | 1.4 | 1.02 | 2.6 | 0.37 | 7,503 |
| Chicago Lying-in | 0.35 | 5.8 | 7.21 | 1.2 | 0.24 | 5.4 | 0.37 | 14,864 |
| Cleveland, O. | 0.29 | --- | 9.41 | --- | 0.60 | --- | 0.87 | 9,274 |
| Great Falls, Mont. | 0.24 | 40.0 | 0.24 | 0 | 0.83 | --- | --- | 2,045 |
| Lincoln, Neb. | 0.06 | --- | 2.93 | --- | 1.91 | --- | --- | 1,675 |

TABLE IV

| PLACE | NUMBER OF DELIVERIES | INCIDENCE OF—PER CENT | | | |
|--------------------|----------------------|-----------------------|------------------------|-------------------------|--------------------|
| | | ECLAMPSIA | NON-CONVULSIVE TOXEMIA | HYPER-EMESIS GRAVIDARUM | ABRUPTIO PLACENTAE |
| United States | 276,221 | 0.66 | 4.13 | 0.87 | 0.54 |
| British Islands | 99,253 | 1.13 | 10.88 | 1.48 | 1.82 |
| Europe | | 0.68 | *4.40 | *1.00 | *0.94 |
| Asia, Africa, etc. | 1,876,961 | 0.52 | 0.52 | 0.19 | 0.17 |
| Mean for all data | | 1.00 | 5.10 | 0.89 | 0.87 |

*One German Clinic.

Our figures for many of the hospitals in Asia, India, Africa, etc., are really not comparable to hospital figures for the United States. There is no prenatal care, and hospital beds are few in number. Thus there occurs the paradox of a lower incidence for nonconvulsive toxemia than for eclampsia. As to hyperemesis gravidarum, only the seriously ill patients would be hospitalized. Abruptio placentae is quite often grouped with placenta previa, and, furthermore, many cases were either not correctly diagnosed while at home or died before they could be taken to the hospital. For these various reasons and because convulsions and edema in the pregnant woman are striking signs, eclampsia was selected as the index for study.

The data from the various countries are of great interest. Eclampsia, toxemia, hyperemesis, and abruptio are either unknown or are very rare among the native women of Kenya, Uganda, the Zulu, Tanganyika, Belgian Congo, Ethiopia, Persia, Java, Hawaii, British Malaya, Alaska, Australia, and date oases of Africa whose habits and diet have not been changed by the white race. In contrast, eclampsia is very common in Algiers, Cape Town, Colombo, and Porto Rico, where the natives have adopted many, if not all, of the diet and other habits of the white. Eclampsia is very rare among the negroes in Africa, but has an incidence among the negroes of 0.71 per cent in New Orleans and 0.92 per cent in Atlanta. Of course, the negro in this country is not of pure strain, but these figures do show the effect of a different diet, habits, climate, etc. Hypertension is also rare in the African negro male and female in contrast to its high frequency in the colored race in this country.

Similarly, eclampsia is uncommon or rare in the country districts of India and China in contrast to the cities where it is very common. Again the chief factor seems to be the adoption by the natives of the habits and diet of the white.

We have been able to gather some statistics as to the incidence of eclampsia during the last century.

Rotunda Hospital, 1826 to 1833: Collins reports 16,654 deliveries with 30 cases of eclampsia, an incidence of 0.18 per cent and mortality of 17 per cent.

Churchill in 1843 collected 159 cases of convulsions in 96,903 labors, an incidence of 0.16 per cent. The maternal mortality ranged from 28 to 70 per cent.

Medical College and Eden Hospitals, Calcutta, 1848 to 1894: Dass reported 10,728 deliveries with 101 cases of eclampsia, an incidence of 0.94 per cent and mortality of 58 per cent.

Many similar figures are available. Eclampsia is probably not increasing. For example, Hauch and Lehmann reported an incidence of 0.10 per cent for rural eclampsia in Denmark between 1918 and 1927. Hinselmann states the incidence in Germany among patients at home is 0.05 per cent. Thus, the figures for the last century, when hospital delivery was rare, are comparable to modern statistics of home delivery.

Dr. William Randall of our Graduate Library School has made a statistical analysis of our meteorologic data and the incidence of eclampsia. Correlation coefficients were figured for the following variables, with the accompanying results:

FOR THE TOTAL STATISTICS

| | |
|---|--------------------|
| Incidence of eclampsia/average temperature | 0.344 ± 0.069 |
| Incidence of eclampsia/range of temperature | -0.240 ± 0.076 |
| Incidence of eclampsia/rainfall | 0.160 ± 0.076 |

The first of these is significant and indicates that temperature is a factor in the occurrence of eclampsia.

Partial correlation coefficients were figured for the incidence of eclampsia against each of the other three variables, holding the two extra variables constant, with the following results.

| | |
|--|--------|
| I.Ec./Average temperature (range and rainfall constant) | 0.285 |
| I.Ec./Range of temperature (average temperature and rainfall constant) | 0.66 |
| I.Ec./Rain (average temperature and range constant) | -0.114 |

The first of these has some significance.

FOR THE UNITED STATES ONLY

| | |
|---|--------------------|
| Incidence of eclampsia/average temperature | 0.442 ± 0.086 |
| Incidence of eclampsia/range of temperature | -0.377 ± 0.091 |
| Incidence of eclampsia/rainfall | 0.198 ± 0.102 |

The first and second are significant, but again temperature is the predominant factor.

Partial correlation coefficients for the United States:

| | |
|--|--------|
| I.Ec./Average temperature (range and rainfall constant) | 0.247 |
| I.Ec./Range of temperature (average temperature and rainfall constant) | -0.004 |
| I.Ec./Rain (average temperature and range constant) | -0.083 |

The first of these has some significance.

Multiple correlation coefficients were figured to determine the chance of predicting the incidence of eclampsia on a basis of the three variables, with the following results:

| | |
|--------------------|-------|
| Total statistics | 0.336 |
| United States only | 0.450 |

These figures indicate that if we knew the meteorologic data for a city, one could predict the probable occurrence of eclampsia and for the world be correct in about 11 per cent and for the United States in about 20 per cent of the cases.

Dr. Randall summarizes as follows: "It appears from the above coefficients that the only factor of possible significance is the average temperature. All of the coefficients, however, are small; further data are obviously required before any stable relationships could be shown. The climate which would seem to be most favorable to the incidence of eclampsia, on a basis of these data, would be one with a high average temperature, a small range of temperature, and a high measure of rainfall—in other words, a hot wet climate."

Meteorologic conditions are not the only factors. The following table taken from Balfour's report illustrates that under the same conditions of climate and temperature other factors, such as race, diet and domestic habits, cause marked differences in the occurrence of eclampsia.

| | BOMBAY HOSPITALS | | ALL INDIA HOSPITALS (LESS BOMBAY) | |
|------------|------------------|-----------------------------|--------------------------------------|--------------|
| | NO. OF CASES | INCIDENCE OF ECLAMPSIA % | INCIDENCE OF ECLAMPSIA % | NO. OF CASES |
| Hindu | 2,066 | .038 | 1.52 | 5,167 |
| Mohammedan | 842 | 1.66 | 2.43 | 1,273 |
| Christian | 801 | 0.37 | 0.69 | 1,152 |

These are, of course, all hospital statistics, but the differences between Hindu, Mohammedan, and Christian are so great that one must conclude that they are significant. The most likely explanation of the greater incidence is that the diet of the Mohammedan contains meat in contrast to that of the Hindu who eats no meat.

Our data also indicate that the race, diet, and personal habits are all of importance when one considers the incidence of these various diseases. It is obvious that until we eliminate these other factors we must acknowledge the fact that Randall's remarks as to temperature and rainfall, which are based on statistics, cannot be regarded as conclusive.

Another pertinent observation is the appallingly high maternal mortality in Africa, Ceylon, India, China, Siam, etc., and what is most remarkable is the fact that the maternal deaths are not due to eclampsia and toxemia. In the United States these two diseases account for 20 to 40 per cent of the maternal deaths, but in the countries listed above, either they are not the cause or the percentage of total deaths caused by eclampsia and toxemia ranges from none to 10 per cent. Vital statistics are notoriously open to error but convulsions, pregnancy, and death are a triad which should be easily recognizable. Therefore, the very fact that toxemia deaths not only form a small part of the total maternal mortality, but are few in actual numbers in Asia, Africa, etc., gives additional confirmation to our data as to the occurrence of eclampsia.

SUMMARY

The geographic distribution of eclampsia, toxemia of pregnancy, hyperemesis gravidarum, and abruptio placentae has been studied. These diseases are peculiar to pregnancy and the incidence should, therefore, be constant throughout the world.

Eclampsia, because of its striking symptoms and signs, has been used as the index. Collected data show that the incidence ranges from 0 in many cities to 2.85 per cent in Algiers, Africa, and 7.2 per cent in Charlotte, North Carolina. The mean incidence for the world is 1.0 per cent, for the United States 0.66 per cent, for the British Isles 1.13 per cent, for Europe 0.68 per cent, and for the rest of the world 0.52 per cent.

The incidence of eclampsia and meteorologic data for various cities have been studied statistically. There is some correlation, especially for the United States, between eclampsia, a high average temperature, a small range of temperature, and a high measure of rainfall.

Our data seem to indicate that eclampsia may and undoubtedly does occur in the native who has had little or no contact with modern civilization. However, the latter with its mental strain and stress, change in diet and habits seems to cause an increase in the occurrence of eclampsia.

Our results warrant further investigation of the geographic distribution of these diseases, as a means of, first, determining pertinent factors, second, eliminating or preventing them, and third, determining their relation to the etiology of the disease in question.

I wish to thank the various doctors, hospital superintendents, and public health officials who cooperated so generously. I appreciate the courtesy shown me by the librarian of the American Medical Association. Dr. R. E. Michener, Kenya, Africa, was most helpful in the collection of data from East Africa.

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It would require too much space to list the many individual references. Therefore, any of the collected material not listed below is on file and is available for reference in the library of the University of Chicago.

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CONGENITAL ABSENCE AND TRAUMATIC OBLITERATION
OF THE VAGINA AND ITS TREATMENT WITH
INLAYING THIERSCH GRAFTS*

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CONGENITAL absence of the vagina results from faulty development or fusion of the Müllerian ducts. Variations in the development of this defect are designated as aplasia, atresia, hypoplasia, and duplication. There may also be various combinations of these states. With entire absence of the vagina there is usually an associated absence or arrested development of the uterus and, not infrequently, of the adnexa. The entire vagina is represented by a fibrous or fibromuscular cord situated between the bladder and the rectum, the uterus usually being maldeveloped, often solid and divided into two parts.

Not all patients who have congenital absence of the vagina should be treated surgically, but only those who are otherwise normally developed and who contemplate marriage. Some patients without a vagina also are without ovaries and therefore show an abnormal balance between prolactin and estrogenic hormone and an associated sexual indifference. Patients who are normal in every other respect but who do not contemplate marriage need not be treated since their health will not be affected by the defect. When patients have married before the existence of the defect became known surgical reconstruction is of course essential. The psychologic basis for surgical interference in such cases is important. In many instances a sex neurosis develops when the patient learns of her condition and she feels she will never be able to take her normal place in society. Occasionally such a patient has resorted to suicide during a period of mental depression. A thoughtful discussion of the subject, in which it is clearly stated that the anomaly is not at all uncommon and can be corrected surgically, does much to appease this mental distress.

Traumatic stricture of the vagina, either partial or complete, is occasionally seen following difficult instrumental delivery incident to extensive sloughing of the vaginal mucosa. It also occurs from external violence, in which case the perineum and rectum may also be injured. In these cases the birth canal and menstrual function have been normal and surgical reconstruction is definitely indicated. If associated injuries to the bladder, urethra, and rectum have also occurred, producing fistulas, surgical reconstruction is necessarily divided into stages and the first stage consists of closing the fistulas and obtaining a continent bladder and rectum.

*Read at a meeting of the New York Obstetrical Society, January 11, 1938, and at the Pan American Medical Association, Pan American Cruise, January 15 to February 1, 1938.

For more than a century, attempts at surgical reconstruction for congenital absence of the vagina and for atresia have been carried out by many different methods and with varying degrees of success.

The first good results were reported by Schubert and by Baldwin who utilized the large intestine. Schubert substituted the rectum for the vagina and reconstructed the rectum by bringing the bowel down and attaching it to the sphincter. Baldwin modified the procedure by bringing down a portion of the sigmoid colon, re-establishing intestinal continuity by end-to-end anastomosis. He later changed this method by bringing down a loop of ileum or jejunum, if the length of the mesentery did not prohibit. It has been observed by those who favor the Baldwin operation that it is unwise to place any undue tension on the vessels of the mesentery which supply the loop intended for the new vagina, since tension invariably leads to thrombosis and loss of vitality of the resected bowel. However, when sufficient length is available to bring the loop to the perineum and there are no other complicating conditions, this operation is one of the most satisfactory ones available for correction of the defect. Judin reported six successful cases in which the Baldwin technic was used without a death. I have personal knowledge of many other successful cases, but also of many failures which have not been reported.

Graves was one of the earliest writers to report good results from pedicle grafts taken from the labia and also from the skin of the thigh by a method which he originated. He reported five cases, covering a thirteen-year period in which patients had been so treated. Four of the patients had normal secondary sex characteristics. Since the labia in many cases are quite small, making it almost impossible to perform Graves' operation, modifications were advocated by Frank and Geist. They formed a tubular graft taken from the thigh and later placed it in the new vaginal site. Grad later introduced modifications of the tubular graft, the purpose of which was to maintain greater blood supply and thereby guard against later necrosis.

Although many good results have been reported following the use of these skin and pedicle grafts, they have many disadvantages, chief among which is subsequent secondary contraction which will invariably ensue unless some method is substituted to prevent it. This can be overcome, however, by constant dilatation during a period of four to six months, which can best be accomplished by a retained mechanical dilator. Another distinct disadvantage is the prolonged hospitalization and repeated operations necessary to correct the defect by multiple stage procedures. This entails considerable expense to the patient and furthermore makes it unwise for anyone to attempt the procedures if he is not familiar with plastic surgery and with the use of pedicle grafts.

McIndoe, who was cognizant of the disadvantages associated with pedicle grafts as a routine method and of the fact that the risk involved in using any part of the intestinal tract was perhaps too great to assume in correcting a defect which of itself was not a hazard to life, suggested a simple method of utilizing a large Thiersch graft taken from the thigh and implanting it into the vaginal position.

In brief this procedure consisted in first opening the space between the bladder and rectum up to the reflection of the peritoneum. This latter structure was then pushed upward to add depth to the new tract. A solid rubber mold was constructed to conform to the depth and diameter of the new vagina, which usually measured 4 by 1½ inches (10 by 3.8 cm.). A Thiersch graft of sufficient size to cover the rubber mold completely was then cut in one piece from the skin of the thigh. This graft was then sewed on the mold with catgut sutures. The mold carrying the graft was then carefully placed within the vaginal tract and held firmly in this position

for several weeks. At the end of this period the mold could be removed and the vaginal canal was at this time completely covered with a thin layer of epithelium and closely resembled a normal vagina in every respect. Although Kirschner and Wagner and others in Germany who used a similar method had reported excellent results in most cases, there were a few cases in which contraction later produced some difficulty. They emphasized the point, however, that dilatation should be continued by the patient for a considerable time. The entire procedure was performed in one stage and the period of hospitalization rarely exceeded three weeks. The surgical risk was also reduced to a minimum.

In order to overcome the inconvenience to the patient which is caused by the necessity of wearing a vaginal dilator constantly, McIndoe recommended complete closure of the vulva over the mold and skin graft, but provided a small opening in the perineum for drainage. At the end of a six-months' period the contraction phase had passed and the vulva could be opened and the mold removed without fear of secondary contraction. He claimed no inconvenience to the patient from keeping the mold in position in this manner.

I have further modified this method by utilizing a flexible rubber tube, over which the graft is placed, instead of a solid rubber mold. The rubber tube can be cut to any desired length, which is necessary because of the fact that the distance between the peritoneum and the peritoneal reflection is variable in cases of congenital absence of the vagina. In my method the rubber tube is removed in from ten to fourteen days and is replaced by a bakelite sound, which is made especially for each patient. A sanitary belt is worn by the patient; this belt fits firmly around the neck of the sound which maintains it in constant position. The sound is worn continuously for six months, being removed once a day for cleansing purposes.

In the past fifteen months I have used this method in five cases of congenital absence of the vagina and in two of stricture of the vagina following delivery, in all instances with good results. The skin grafts have been cut by my colleagues in plastic surgery, Dr. Figi and Dr. Havens.

REPORT OF CASES

CASE 1.—An unmarried girl, 17 years of age, came to the clinic on March 29, 1937, complaining that she had never menstruated. Two years previously she had begun to have periodic pelvic pains each month, and just before these occurred there was some headache and backache, and swelling and pain in the breasts. In December, 1935, she was examined and absence of the vagina was found. Reconstruction was attempted in January, 1936, elsewhere, but was not completed.

On examination at the clinic the patient weighed 119 pounds (54 kg.) and was of good physical development. Her breasts were firm and somewhat large for her age. The vulva and clitoris were normal but the vagina was only about $\frac{1}{2}$ inch (1.3 cm.) in length. Cystoscopic examination showed a rather large bladder with slight reduction in expulsive force. No abnormal openings could be demonstrated. Both ureteral orifices were somewhat gaping, but the urine from each side was normal. A diagnosis was made of congenital absence of the vagina. On April 5, the tissue between the bladder and rectum was separated up to the reflection of the peritoneum. An inlying split Thiersch graft was then placed in position after the method described. Ten days later the vaginal tube was removed and the grafts were inspected. The tube was replaced by a vulcanite splint, which was to be left in position for six months.

CASE 2.—A married woman, 38 years of age, registered at the clinic on June 14, 1937, complaining that she had never menstruated. She had been married for eighteen years. She had never been pregnant. In 1914 she had had her appendix removed and it was found that she had no uterus.

The patient's general physical development was normal. No uterus could be felt on rectal examination, the clitoris was somewhat enlarged and there was an absence of the vagina. On June 29, an inlying split Thiersch graft was placed in position according to the method described. Ten days later the tube was removed and replaced by a bakelite vaginal dilator. The entire vaginal tract was completely epithelized. The patient returned to the clinic four months later, at which time the vagina measured 4 inches (10 cm.) in depth and 1½ inches (3.8 cm.) in diameter with a normal introitus.

CASE 3.—An unmarried woman, 18 years of age, registered at the clinic on May 24, 1937. She said that she had never menstruated but that she had had periodic headaches each month and her breasts had become swollen. There was no abdominal pain at any time. She had been married only a few months when her marriage was annulled.

On physical examination at the clinic the patient was found to be well developed. Her breasts were normal in size. On rectal examination no pelvic organs could be demonstrated. There was a complete absence of the vagina. No estrin or prolan could be demonstrated in the urine by the Frank technic. The basal metabolic rate was -16 and -17 per cent on two consecutive tests. The patient weighed 164 pounds (74.4 kg.). A diagnosis was made of congenital absence of the vagina and hypothyroidism with endocrine dysfunction. On May 28, reconstruction of the vagina was carried out, utilizing an inlying split Thiersch graft after the method described. Fourteen days later the rubber tube was removed and replaced by a bakelite sound. The vagina was completely epithelized. Examination on Dec. 5, 1937, revealed a normal appearing vagina.

CASE 4.—An unmarried woman, 26 years of age, registered at the clinic on July 30, 1937, stating that she had never menstruated and had had no signs corresponding to those associated with menstruation. Her appetite was good. She had lost 30 pounds (13.6 kg.) in the past two years which she attributed to dieting.

On general physical examination the patient was found to have a normal feminine habitus and well-developed breasts. The labia were somewhat hypertrophied and the vagina was represented by a small indentation. The uterus could not be palpated on rectal examination, but a normal-sized ovary could be felt on the right side. The urinary estrin was positive (33 rat units for twenty-four hours). A diagnosis was made of congenital absence of the vagina. On August 10, reconstruction of the vagina was carried out, utilizing an inlying split Thiersch graft. Fifteen days later the tube was replaced by a bakelite vaginal dilator to be left in position for six months. The vagina was completely epithelized.

CASE 5.—An unmarried girl, 17 years of age, registered at the clinic on Nov. 15, 1937, stating that she had never menstruated, but had had sacral backache and some low abdominal pain associated with nausea and vomiting each month. Her general health had been good.

On physical examination she appeared to have a normal feminine habitus with well-developed breasts. Her weight was 128 pounds (58.1 kg.). On rectal examination she was found to have no vagina. Both ovaries could be palpated, although they were smaller than normal. While a cervix or uterus could not be palpated, a shelf or broad band could be felt in the position of the uterus. No urinary estrin could be demonstrated. A diagnosis was made of congenital absence of the vagina. Reconstruction was carried out on November 16, according to the technic described. Ten days later the tube was removed and replaced by a bakelite sound which was to be worn for six months. The vagina was completely epithelized with the exception of a small area in the vault.

CASE 6.—A married woman, 20 years of age, registered at the clinic on June 4, 1936. Two months prior to registration she had undergone instrumental delivery of a large baby. She was in labor twelve hours, a face presentation necessitating craniotomy. The patient's convalescence had been rather stormy and there was considerable fever. Fourteen days after delivery urine began to leak through the vagina.

On examination the patient's general physical condition was found to be good except that she was totally incontinent and there was considerable scarring of the perineum. Cystoscopic examination under anesthesia showed the urethra to be practically destroyed; the index finger could be inserted into the bladder through the site of the urethra. The sphincter was still present, although it was markedly weak. The bladder appeared normal and clear spurts of urine could be seen coming from both ureteral orifices. Pelvic examination at this time showed the posterior vaginal wall to be lacerated and healed by dense scar tissue, which narrowed and shortened the vagina. The cervix was not palpable and there seemed to be a small fistulous tract running up to it on the right side. Operation was advised but the patient deferred it.

One month later the patient returned to the clinic for surgical treatment. At operation, on August 17, I was able to separate the anterior vaginal wall up until I could feel the cervix through the tissues, although I could not find an opening into the cervix. The vagina, except near the cervix, had been obliterated by sloughing of the mucosa. About $1\frac{1}{2}$ inches (3.8 cm.) of the posterior vaginal wall near the cervix appeared normal. This was elevated and sutured to the skin of the labia minora. The vaginal canal was then packed with gauze, the urethra was partly reconstructed and one retention catheter was placed in the bladder. The patient was then given vaginal dilators and advised to use them daily, following her dismissal from the clinic, in order to overcome the contraction. The urethral sphincter became completely continent and she was able to void normally. The vagina, however, became practically occluded by scar tissue.

The patient was readmitted to the hospital on March 22, 1937, for reconstruction of the vagina. An inlying split Thiersch graft over a rubber tube was utilized after the method described. The bladder was again separated from the rectum by cutting through the scar tissue. At this time I was able to identify the cervix and the cervical canal. It was opened and the uterus was curetted. A Baldwin tube was then placed in the cervix and held in position by a silkworm suture. A split Thiersch graft was placed over a rubber tube, which measured 4 inches (10 cm.) in length, and this was fitted snugly into the vagina around the cervix and left in position for two weeks. Fourteen days later the Baldwin tube was removed because the patient was menstruating and the rubber tube was removed and replaced by a bakelite sound. The vaginal tract was almost completely epithelized except near the cervix on the anterior vaginal wall. The scar tissue to the left of the broad ligament remained somewhat sensitive and there was some constriction around the cervix. The patient has menstruated at regular intervals since, although she does have some pain. Her sex life is satisfactory, but she has been advised against further pregnancies.

CASE 7.—A married woman, 19 years of age, registered at the clinic on June 9, 1937, complaining of pain in the right side of her chest. On May 2 she had been delivered of a baby and following this had had chills and fever. She had been given four transfusions and intravenous medication. Blood cultures were negative. The patient had returned home but, after two days, sudden pain developed in the left side of her chest associated with coughing, chills, and fever. Her temperature was 106° F. The patient also complained of pain in the right lower abdominal quadrant.

On physical examination at the clinic a pelvic mass was found on the right side which extended above the crest of the ilium. In addition there was evidence of an embolic pneumonia on the right side. The patient was hospitalized and 500 c.c. of light brown fluid were removed from the left pleural cavity. Three weeks later 500 to 600 c.c. of pus were drained through a small incision in the right lower abdominal quadrant. The patient was then given two blood transfusions and recovery was uneventful.

The patient was re-examined on Nov. 3, 1937. There was no evidence of pelvic abscess, but there was complete atresia of the vagina. She had not menstruated since delivery of her child, nine months previously, and had had no symptoms of abdominal distress relative to menstruation. We were unable to make out the position of the uterus. On November 4, the scar tissue in the old vaginal tract

was incised, gradually separating the bladder and rectum, which were completely adherent. The reflection of the peritoneum was observed. There was no evidence of vaginal epithelium anywhere, so that a completely new vagina was made by an inlying graft after the method described. The cervix could not be identified. Eleven days later the tube was removed and the tract was almost completely epithelized. A bakelite vaginal sound was placed in position; this was to be worn for six months. Six weeks later examination of the vagina showed it to be of normal depth and diameter and to be completely epithelized except around the region of the cervix. The patient had by then had one menstrual period, and on examination I could visualize blood oozing through one spot in the vault of the vagina which probably represents the cervix. This is to be dilated and reconstructed at a later date.

COMMENT

I rather suspect that the incidence of congenital absence of the vagina is much greater than was formerly believed because there must be some who fail to seek treatment and the cases of many who do seek treatment are not reported in the literature. Some who do seek treatment refuse the abdominal operation because of its magnitude, and some, even though they are most anxious to have the defect corrected, hesitate to submit to the multiple stage procedure with the repeated trips to the hospital which are necessary when pedicle grafts are used.

Simplicity in surgery leads to more successes than do complicated operations; the mortality rate drops and the field of applicability becomes greater to more surgeons, so that the patients always benefit by it. I believe it can safely be stated that patients with congenital absence or atresia of the vagina no longer need fear the operation necessary to correct it. The procedure can be carried out by any surgeon familiar with skin grafting.

McIndoe has contributed enormously to the success of this operation by determining the period of contraction which is common to most cases in which an epithelized canal is constructed. If this period of contraction is disregarded, the operation becomes a failure. The contraction phase is, I believe, longer in cases of traumatic stricture than in those of congenital absence, since in the former, one is dealing primarily with a field of scar tissue. I have recommended, therefore, that the dilator be kept in position nine months instead of six months.

Patients are almost always interested in the degree of scarring on the thigh from removal of the graft. If the graft is accurately cut as a Thiersch graft, there is practically no scar at all, but if the full thickness of the skin is inadvertently taken, a scar will result. When it does develop, radium therapy has accomplished much in eradicating the scar tissue.

The surgical management of stricture is much more difficult than that of congenital absence of the vagina. Extreme care must be exercised to avoid injury to the urethra, bladder, and rectum, since it is necessary to form the new vaginal tract by sharp dissection through the dense, and too often inflamed, scar tissue. Also, fistulas to the surrounding organs may have been previously closed, and recurrence of these can be avoided only by exercising extreme caution. The cervix should be located if possible so that the patient can again menstruate. If this is not practical, owing to extensive trauma, then hysterectomy is in order. Baldwin

performed it in one of his cases of stricture. In both of my cases of stricture the patients are menstruating, and in one I have some further plastic work to do on the cervix. When the cervix can be located, it is pulled into the rubber tube over which the graft is placed. This can only be done over a flexible rubber tube, as I have suggested. The grafts then grow over the anterior and posterior vault leaving the cervix exposed. If the cervix cannot be definitely exposed, then the end of the tube should be placed in the region of the cervical os, and it should not be covered by the skin graft. Later, blood may be seen making its appearance from a small aperture in the vault, and the cervical canal can then be definitely located and dilated. Stricture of the canal, if present, is handled by repeated dilatations.

SUMMARY

A brief review of the operative procedures for the correction of congenital absence or traumatic stricture of the vagina is presented. Some of the disadvantages associated with pedicle grafts and the risk involved in using any part of the intestinal tract are stressed. The McIndoe procedure is the operation of choice by reason of its simplicity and practicability. I have added certain modifications to this procedure which seem to me to be sound and useful.

Five patients with congenital absence of the vagina and two with traumatic stricture of the vagina were treated successfully and without mortality by this method.

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Leucoplakia, kraurosis, neurotic pruritus and atrophic vulvitis are various names given to conditions which are the results of the same deficiency. According to Swift, this deficiency is due to a lack of absorption of vitamin A, caused by a varying degree of achlorhydria. He observed a series of women with intractable pruritus associated with achlorhydria and other signs of a deficiency of vitamin A. The addition of dilute hydrochloric acid to the normal diet (one teaspoonful in a glass of water) relieves as a rule the pruritus and other vulvar affections. Half of this solution is to be sipped during and the other half drunk after each meal.

Vitamin A in the form of cod liver oil should also be given. It is suggested that excision of the vulva is not necessary except in cases in which there is suspicion of a malignant change. Epithelioma of the vulva should become increasingly rarer if this chronic irritation is relieved at any early stage. Achlorhydria is often present in cases of pruritus vulvae in which the irritation has not been relieved by treating the supposed primary cause.

J. P. GREENHILL.

THE DILATING BAG IN OBSTETRICS*

ITS USE, ABUSE AND HAZARDS

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THE purpose of this paper is not to extol the virtues of one particular method of inducing labor, but rather comprehensively to consider the dilating bag, that it may be judiciously employed with the operator fully cognizant of its insufficiencies and the accidents attending its use.

Cesarean section unquestionably is not the answer to all obstetric difficulties, nor the routine method for terminating labor. Medical induction of labor is successful in a sufficient majority of instances to warrant its trial when the need is evident. When medical induction fails, recourse must be made to mechanical means. The two common forms in present day use are (1) artificial rupture of membranes and (2) intrauterine insertion of the dilating bag. It is the second method with which we are concerned, and the bag used is the Voorhees' modification of the Champetier de Ribes'.

The use of the bag is neither recent nor new. An early form was devised by Braun in 1851 and Champetier de Ribes described his in 1888, giving considerable impetus to its use. Dangers and defects inherent in the mechanical construction of bags in use were not overcome until Voorhees modified the de Ribes' bag in 1897 and published in 1913 experiences in 634 inductions at Sloan Hospital for Women. Since then, the bag has had wide usage, judging from published reports, but there seems to be a marked recession in recent years, even at Sloan. Following a preliminary reading of our experiences two years ago, the incidence has diminished in our own experience. It is possible that some cogent reasons for this may be revealed in this study, which details pertinent data concerned with the use of the Voorhees' bag in obstetrics in 372 cases occurring in 25,969 parturitions at the Margaret Hague Maternity Hospital, an incidence of 1.4 per cent.

INDICATIONS

The conditions indicating the use of the bag are given with their frequency in Table I. It is observed that well-recognized indications, such as placenta previa, pre-eclampsic toxemia, abruptio placentae, primary uterine inertia, nephritis and heart disease, account for over 70 per cent of the total.

The soundness of bag induction in inevitable abortion, cervical dystocia, and hydatid mole is open to question. Postmaturity was a convenient indication in 31 or over 8 per cent of the entire group. It is only fair to state that nearly half of these were done "experimentally" during studies on intrauterine hydrostatics during labor pains. In older publications contracted pelvis occupied a prominent place as a cause for bag induction. This is not so in our experience nor should

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it be so. The outcome is too uncertain for the fetus, and the jeopardy to the mother too great to permit it to be commonly accepted as a suitable indication for bag insertion.

Observations on the selection of the bag disclosed the following data. The No. 5 and No. 6 Voorhees' bag was used 241 times or 65 per cent of the total. The smaller bags, No. 2, No. 3 and No. 4, were used 131 times in all or 35 per cent. Disregarding the influence of other factors, this shows a marked tendency to utilize large bags when any are indicated, a tendency which is neither invariably safe nor wise. After considering all pertinent data No. 4 and No. 5 bags are believed to be the most valuable in common use.

TABLE I. INDICATIONS FOR 372 BAG INDUCTIONS IN 25,969 DELIVERIES—INCIDENCE 1.4 PER CENT

| | CASES BAGGED | |
|--|--------------|----------|
| | NO. | PER CENT |
| <i>Pregnancy Diseases:</i> | | |
| 1. Placenta previa | 60 | 16.1 |
| 2. Pre-eclampsia | 72 | 19.3 |
| 3. Eclampsia | 6 | 1.6 |
| 4. Abruptio placentae | 32 | 8.6 |
| 5. Primary uterine inertia | 25 | 6.7 |
| 6. Intrauterine fetal death | 16 | 4.3 |
| 7. Cervical dystocia | 4 | 1.1 |
| 8. Premature rupture of membranes | 13 | 3.5 |
| 9. Malpresentation, 4 transverse, 1 face | 6 | 1.6 |
| 10. Polyhydramnios | 5 | 1.3 |
| <i>Postmaturity</i> | 31 | 8.3 |
| <i>Contracted Pelvis</i> | 9 | 2.4 |
| <i>Intercurrent Diseases:</i> | | |
| 1. Nephritis | 65 | 17.4 |
| 2. Heart disease | 17 | 4.6 |
| 3. Syphilis | 11 | 3.0 |
| 4. Hypertension | 6 | 1.6 |
| 5. Pyelitis | 3 | 0.8 |
| <i>No Reason</i> | 15 | 4.0 |
| <i>Others:</i> Miscarriage (4), fetal monstrosity (2), diabetes (2), upper respiratory infection (2), ovarian tumor (2), breech, mole, pernicious vomiting, chorea gravidarum, syphilitic psychosis, tuberculosis. | | |

The patients were considered in five-year age-groups to determine the effect of age upon the hours in labor. Patients in the age-groups over thirty were as prompt in response to bag induction and expelled the bag within time limits as efficiently as the age-groups between 15 and 30. The age of the patient was no factor in anticipating the promptness of response nor the rapidity of labor.

There were 84 primiparas, comprising 22.6 per cent of the total; multiparas, 288 or 77.4 per cent. More than half of the multiparas were over thirty years of age. Only 17, or 20 per cent, of the primiparas were over 30 when induced by bagging.

The smaller bags were retained longer than the larger. The No. 3 bag was retained more than twelve hours in 37 per cent of the times used, the No. 4 bag, 20.6 per cent and the No. 5 bag, 20 per cent. The No. 6 bag in 33 per cent. There seems to be a tendency for labor to ensue earlier and progress more rapidly when No. 4 and No. 5 bags are used.

The cervix was soft and either partly effaced or dilated in most instances, although occasionally a large bag was inserted through a long undilated cervix. This is not good practice.

METHOD OF INTRODUCTION AND USE OF WEIGHTS

While it was impossible to keep accurate data relating to intra- or extraovular bag emplacement, it was recorded that the membranes were artificially ruptured in the first stage in over 50 per cent of the cases. The recommended procedure was extraovular insertion except for placenta previa, but frequently the membranes were accidentally or deliberately ruptured, doubtless partly accounting for some of the 32 cases of prolapsed cords. The wisdom of rupturing the membranes purposely in conditions other than placenta previa or abruption of the placenta is questioned.

The use of weights was considered and the effects noted. They were found to be useless as accelerators of labor, and of no value except under two conditions: in assisting placental tamponade in placenta previa, and in keeping a small cervix filled where an oversize bag had been introduced. Then $1\frac{1}{2}$ or 2 pound weights were employed over a properly adjusted pulley. The use of weights always increased the patient's discomfort considerably and increased the frequency of cervical lacerations. They tended to drag the dilator through an unprepared cervix which failed to efface and retract as it dilated and frequently closed down as soon as the bag was expelled.

ANESTHESIA

Operative delivery followed bag induction in nearly 50 per cent of the 372 cases. This meant double anesthesia danger, if anesthesia were used for the introduction of the bag. It was found that those with *most experience* in bag introduction used anesthesia with the *least frequency*. The only condition which required its use with seeming unanimity was the seldom justified insertion through a long hard or undilated cervix. Comprehensive knowledge of technic of introduction coupled with gentleness and sympathetic assurance adequately supplant the anesthetist.

OBSERVATIONS AFTER INSERTION

After insertion, labor contractions were initiated in 55 per cent of the cases within one hour, and lasted an average of 10.4 hours in all cases. Where the bag was expelled within 12 hours, the average was 5.7 hours; within 18 hours, 7 hours; and within 24 hours, 7.8 hours. The likelihood of failure materially increases after the 12-hour period has passed, the gross 4.5 per cent rising to 20 per cent of failures in patients laboring beyond 12 hours. This fact acquires greater significance when it is recalled that the morbidity rate in patients requiring operative termination of labor increases rapidly after the first 12 hours of labor have passed.

Oxytocics were used in but few cases, pitocin being employed in 3 minim doses. Latterly, pitocin was given in 3 minim doses at half-hour intervals to maintain or restore contractions after expulsion of the bag. The drug is always given hypodermically and never in excess of 3 minim doses, the hypodermic use being selected over other methods of introduction in the belief that a definite measured dosage of known absorption is preferable to other routes where the degree of absorption leaves the operator in some uncertainty as to the exact amount that was absorbed. The circumspect use of this drug was of definite value where failure might otherwise have been expected.

The bag advance was checked and the bag deflated and removed after expulsion through the cervix. In the first 244 cases of bag induction, vaginal examinations were made upon only 20 per cent of patients after bag expulsion. The revelation that this omission in technic cost the lives of several babies is of sufficient merit to justify this entire study.

COMPLICATIONS

Hazards were noted with respect (1) to those inherent in the bag, (2) to the patient, and (3) to the fetus.

Rupture of the bag occurred once from overexpansion, and leakage occurred three times, without resultant damage. The cervix was found to be injured in many cases where operative delivery followed bag induction, but severe cervical damage was noted in but 9 patients. The use of weights increased the incidence of cervical damage. Twice uterine tetany ensued when a large bag was inserted through a hard, closed cervix, the upper segment apparently became overactivated and over-irritated, with the lower failing to expand and retract.

TABLE II. RELATIONSHIP OF SIZE OF BAG AND PARITY TO COMPLICATIONS

| BAG SIZE | TIMES USED | CORD PRO- LAPSE AFTER BAGGING | PROLAPSE OF ARM | DISPLACEMENT WITH CHANGE OF PRESENTATION | INFECTION DUE TO BAG (?) |
|------------|------------|-------------------------------------|--------------------|---|--------------------------------|
| 2 | 9 | | | 1 | |
| 3 | 24 | | | 2 | |
| 4 | 98 | 6 | 1 | 7 | 4 |
| 5 | 201 | 20 | 5 | 20 | 9 |
| 6 | 40 | 3 | 1 | 4 | 1 |
| Total | 372 | 29 (8%) | 7 | 34 (9%) | 14 |
| Primiparas | 84 | 8 | 2 | 9 | 5 |
| Multiparas | 288 | 21 | 5 | 25 | 9 |

The danger to the mother's soft parts, especially cervix and perineum, is largely due to the 50 per cent incidence of operative termination of the second stage of labor which this series showed. Rupture of the uterus through use of a large bag was not encountered, but the danger is real, if bags are improperly used at the third or fourth month of pregnancy. This was done four times in this series, and represented inadequate appreciation of the purpose and use of the dilating bag. The likelihood of morbidity and the often serious problems aroused by the failure of the uterus to respond are substantial hazards. The bag failed 14 times, or 3.7 per cent, and six of these patients had cesarean sections. Such gross errors in judgment obviously increase maternal risk. Forty-six cases or 12.3 per cent were morbid. It is doubtful if this morbidity percentage can be materially lessened inasmuch as all of these bag inductions were performed under most rigid operating room aseptic technic. It is only fair to direct the attention to the fact shown in Table III that more than 25 per cent of these morbid cases were determined only by aberrations in temperature over the allotted 100.4° F. on two readings after the first day. Twelve patients in this group showed no clinical or laboratory signs indicating any sepsis either relating to the bag or to the patient systemically, but are nevertheless classified because of their temperature reading. Many of the other causes for morbidity, as noted in Table III, cannot be ascribed or connected to the use of the bag. There were 9 maternal deaths or 2.4 per cent, occurring within twelve days of delivery. With one exception, the cause of death was the indication for inducing labor. One severe chronic nephritic patient succumbed four hours after a second bag induction, after having unsuccessfully entertained the first for twenty-four hours.

TABLE III. MORBIDITY

| Total of Morbid Cases | 46 or 12.3% |
|------------------------------|-------------|
| <i>Causes of Morbidity:</i> | |
| 1. Not determined | 12 |
| 2. Endometritis, foul lochia | 18 |
| 3. Intrauterine fetal death | 5 |
| 4. Thrombophlebitis | 2 |
| 5. Pyelonephritis | 3 |
| 6. Carbuncle of thigh | 1 |
| 7. Bronchial asthma | 2 |
| 8. <i>B. coli</i> septicemia | 1 |
| 9. Retained placenta | 2 |

Other management might have temporarily spared this patient, and possibly two others with abruption of the placenta.

The baby's life was imperiled by many contingencies. The cord prolapsed in 32 cases, with a loss of 23 babies, 18 after bag induction. Of 121 fetal deaths, 64, or 53 per cent, followed induction of labor with the Voorhees' bag. Excluding nonviable prematures, miscarriages, monstrosities, and those dead before introduction of the bag, there were 29 fetal deaths, or 7.7 per cent, an appreciable number.

The fetal position changed in 34 patients after bagging, an incidence of 9 per cent, and the fetus succumbed in 9 of these. Only thrice was the change of position more favorable for delivery.

TABLE IV. COMPLICATIONS 372 BAG INDUCTIONS

| COMPLICATION | BEFORE BAGGING | AFTER BAGGING | TOTAL | FETAL DEATHS | | TOTAL |
|------------------------|----------------|---------------|-------|----------------|---------------|-------|
| | | | | BEFORE BAGGING | AFTER BAGGING | |
| Prolapsed cord | 3 | 29 | 32 | 5 | 18 | 23 |
| Change of presentation | | 34 | 34 | 1 | 8 | 9 |
| Pelvic infection | | 14 | 14 | 1 | 3 | 4 |
| Hemorrhage | 11 | 2 | 13 | 4 | | 4 |
| Prolapsed arm | 3 | 4 | 7 | 3 | | 3 |
| Retained placenta | | 5 | 5 | 2 | 1 | 3 |
| Shock | 1 | 3 | 4 | | 1 | 1 |
| Secondary anemia | 3 | 20 | 23 | | 2 | 2 |
| Lacerations, 2° | | 18 | 18 | | 1 | 1 |
| Lacerations, 3° | | 3 | 3 | | | |

Twin pregnancy (3), deep cervical laceration (2), thrombophlebitis of legs (2), bronchopneumonia, breast abscess, asthma, vulvar infection, furuncle of thigh, rectovaginal fistula (old), acute nephritis.

TABLE V. OPERATIVE INTERFERENCE

| | |
|-------------------------------|----|
| 1. Forceps: | |
| Low | 31 |
| Mid | 15 |
| 2. Version and extraction | 92 |
| 3. Breech extraction | 28 |
| 4. Cesarean section | 6 |
| 5. Craniotomy | 5 |
| 6. Manual removal of placenta | 2 |
| 7. Vaginal cesarean section | 1 |

180—48.4 per cent

Membranes artificially ruptured in over 50 per cent of cases in first stage of labor, not good practice!

TABLE VI. MORTALITY

| CASE | MORTALITY | DEATH FOLLOWED IN |
|------------------------------|--|-------------------|
| 102 | Eclampsia | 24 hours |
| 769 | Cerebrospinal syphilis | 5 days |
| 1,488 | Chronic nephritis, cerebral apoplexy | 12 hours |
| 13,166 | Chronic nephritis, chronic cardiac disease | 8 days |
| 1,418 | Chronic nephritis, 2 baggings | 4 hours |
| 11,496 | Chronic nephritis, abruptio placentae | 7 hours |
| 7,276 | Abruptio placentae, placenta previa | 24 hours |
| 14,966 | Uteroplacental apoplexy | 6 hours |
| 1,013 | Uteroplacental apoplexy | 10 hours |
| Total—9 deaths—2.4 per cent. | | |

TABLE VII. FETAL DEATHS

| | | NO. | PER CENT |
|---|--|-----|----------|
| Prior to bagging | | 57 | 15.3 |
| Following bag induction | | 64 | 17.2 |
| Total | | 121 | 32.5 |
| Monstrosities, nonviable prematures and fetal deaths prior to bagging | | 92 | |
| Corrected fetal deaths | | 29 | 7.8 |

| CAUSES | | CAUSES | |
|--------------------|----|-----------------------|----|
| 1. Prematurity | | 2. Abruptio placentae | 22 |
| Under 7 mo. | 27 | 3. Placenta previa | 16 |
| 7-8 mo. | 26 | 4. Toxemia pregnancy | 31 |
| 8-8½ mo. | 15 | 5. Chronic nephritis | 17 |
| All under 2500 gm. | | 6. Syphilis | 3 |
| 2. Neonatal | | 7. Malfetation | 2 |
| First day | 8 | | |
| Second day | 3 | | |
| Third day | 4 | | |

COMMENT

Clinical interpretation of the foregoing data has served to clarify and compose our position with respect to Voorhees' bag induction of labor. It is too valuable to be either disregarded or misused. The purpose of a bag is either to stimulate the uterus to contraction through irritation of the lower uterine segment, and effect cervical dilatation and effacement, or to cause these plus tamponade to check hemorrhage in placenta previa. It may occasionally be used to retain a replaced prolapsed cord. It is most useful at term, with the cervix softened and partly effaced and least valuable earlier in pregnancy when the cervix is long and tight. The bag must fit the cervix, and while small bags are attended by a greater likelihood of long labor or failure, there is less risk of prolapsed cord or displacement of presenting part. If the membranes are intact, it must always be placed extraovularly, except in placenta previa. With the exception of placenta previa, the size of the bag chosen depends upon the indication, the part presenting and the condition of the cervix, although No. 4 and No. 5 give the best results in general. No traction is used except in placenta previa, unless the bag tends to slip upward. The bag must be filled until the stem is tense, for if partly filled it will slip into the vagina. In placenta previa, the largest bags that can be safely introduced are ones that most effectively tampon the bleeding area.

Since labor ensues early and with stronger pains than usual, the progress of the bag must be checked constantly by rectal examinations, and abdominal examinations made for change in uterine tension and fetal position. As soon as the bag is through the cervix, its function is completed and it is removed. A vaginal examination must be made immediately to look for prolapse of cord and malpresentation, the two most frequent causes of stillbirths. Either complication compels prompt delivery if the cervix is completely effaced and dilated or easily dilatable. Hemorrhage from placenta previa after bag expulsion likewise forces prompt action, and version-tamponade is the usual procedure of election.

If the uterine contractions cease with the expulsion of the bag, hypodermic pitocin in one to three minim doses at half hour intervals is indicated; none are given after resumption of pains, and larger doses are absolutely prohibited. If conditions are favorable, expectant observation should take precedence over operative manipulations, with their high morbidity and fetal mortality.

CONCLUSIONS

1. Experiences accompanying the use of the Voorhees' dilating bag in 25,969 deliveries with an incidence of 1.4 per cent are recounted.
2. Bag induction of labor is a valuable adjunct to manipulative obstetric practice, with clear-cut indications which one cannot refute.
3. The factors of pregnancy duration, parity, size of bag, insertion with respect to membranes, and use of weights have a direct bearing upon the events subsequent to bag insertion.
4. A proper technic permits introduction without anesthesia, an important actuality in view of imperative anesthesia accompanying the nearly 50 per cent operative incidence subsequent to bagging.
5. The outstanding fetal hazards are prolapse of cord and production of malpresentation, with high fetal death rate.
6. Those who use the dilating bag should be aware of its proper indications and its hazards and know and practice proper technic in its application.

I wish to express my very sincere thanks to Dr. James W. Ravenscroft, Medical-Dental Building, San Diego, California, and Dr. Elbridge E. Anderson, 234 Doctors' Building, Nashville, Tennessee, who materially assisted in the compilation of data used in an unpublished paper covering 12,000 deliveries, which forms part of the present publication.

DISCUSSION

DR. WILLIAM E. CALDWELL.—Gradually, induction of labor with the Voorhees' bag has become unpopular. Other methods have been developed, chiefly the use of pituitrin and the early rupture of the membranes. I fear that these also complicate what should be a normal labor, unless the doctor has excellent judgment as to the time of induction and skill enough to get out of trouble when it occurs. Induction of labor to get a small, premature baby through a small pelvis is seldom advised. The number of labors induced for this reason which have been unsatisfactory, the large percentage of operative deliveries, and the well-recognized truth that a premature baby does not stand a difficult labor or operative procedure well, have led to leaving the woman alone until she goes into labor. Then, if necessary, the delivery may be terminated by a low-flap cesarean section or extraperitoneal operation.

The fear of postmature babies, which was a common indication for induction of labor, has been decreased by the knowledge that very few babies actually are postmature. Complications endangering the life of mother or child are well handled with induction of labor if the lower uterine segment has been formed and a soft, and a dilatable cervix is present.

The chief function of the bag at the present time is to control bleeding in placenta previa. There is no question that the bag works well in controlling hemorrhage and the chief cause of trouble in this method is the need for an immediate delivery after the bag comes through a cervix which is not always completely dilated or retracted. Further labor, or cutting the anterior lip of the cervix, is feasible

and, in the hands of properly trained obstetricians, will give as good results in the immediate pregnancy, and safer deliveries in subsequent pregnancies, than cesarean sections which are now so popular for this condition.

Another use of the bag is in cases where it is impossible to get either the ovum or presenting part well down into the lower uterine segment. It is essential to have something in the lower uterine segment and cervix in order to have adequate labor.

I would criticize the size of the bags which Dr. Waters advocates. Except in some serious cases of placenta previa, a No. 5 bag is seldom indicated. Again, the attachment of weights to the stem, $1\frac{1}{2}$ to 2 pounds or more, causes spasmodic contractions of the uterus, pulls the bag through the cervix, and seldom induces labor properly.

DR. GEORGE H. RYDER.—The dilating bag was used too frequently twenty years ago, and for that reason it fell into disfavor with many obstetricians. Its main uses then were for the induction of labor and for stimulating labor already begun. In both of these indications, pituitrin can now usually be used instead.

There are still, however, certain conditions where the bag can be used to advantage, namely dry labors with rigid cervixes, where pituitrin or thymophysin have been unsatisfactory, and in breech presentations.

In a series of 1,400 consecutive deliveries in private practice I have used the bag 67 times, with a corrected morbidity of 4.47 per cent, and no maternal mortality from puerperal infection. There were two prolapsed cords, in the 67, with one fetal death. No change of presentation or position of the fetus occurred. These two complications result from using a bag too large for the dilatation of the cervix.

DR. SAMUEL A. COSGROVE.—The largest bag that can be introduced through the cervical dilatation present is the best one. My own preference is a No. 4 bag, which can be introduced through a cervix dilatation of one finger. Then the action of the bag is as prompt and certain as it is possible to be. Inasmuch as many of the indications for which the bag is employed themselves jeopardize the child, it is not unreasonable to accept a certain fetal loss, dependent on the inevitable occasional prolapse of the cord and disturbance of position, which I admit the use of those large bags entails. On the other hand if a succession of small bags is used, the infective risk to the mother is definitely increased. As to weighting the bags, I believe that a small weight applied to the tube when a large bag is used is useful to keep the bag in the axis of the vagina, thus permitting it to act efficiently as the uterus contracts behind it.

I would emphasize most strongly what Dr. Waters has said about the necessity of following the bag carefully once it is introduced, and removing it as soon as it has performed its function, in order that any possible complication following its use may be recognized and dealt with.

DR. HARVEY B. MATTHEWS.—I have never put a weight on a bag in the cervix, but I have seen at least two very sad accidents from deep lacerations through the cervix and the lower uterine segment following the use of weights. To advise the general use of a weight attached to a bag in the cervix is certainly not desirable.

In the hands of the expert who knows the size of the pelvis and appreciates the approximate size of the postmature infant, induction might be practiced. I personally would rather let the patient go ahead until labor begins, give her a fair test of labor and accomplish delivery by the use of whatever method seemed indicated at the time.

In regard to the size of the bag, I rarely use one larger than No. 4, very, very occasionally perhaps a No. 5. I have never used a No. 6.

Infection need not necessarily be a hazard in using bags. We have very little if any more morbidity in our bag cases with the use of mercurochrome and hence do not fear infection.

I have only two or three indications for the use of bags. Most important of these is induction in the presence of a severe toxemia and in placenta previa, where cesarean section is not indicated.

Whether you should introduce a bag intraovularly or extraovularly does not make any difference as far as the efficacy of the bag is concerned. Personally I like to keep the membranes intact because there is always a rim of cervix remaining after the bag is expelled and the "forewaters" are helpful in obtaining full dilatation and delivery without undue laceration.

DR. ARTHUR W. BINGHAM.—There are two reasons for the bag falling into disrepute. One is that the indications have increased entirely too much and the other that the size of the bag has increased too much. I never use a bag larger than a No. 3 except occasionally in marginal placenta previa, where I have used a No. 4. I never knew there was a No. 6 until the other day in investigating a death in New Jersey, I found a No. 6 bag had been used and a laceration of the cervix had resulted.

DR. WATERS (closing).—Since presenting a similar analysis in 10,000 cases two and a half years ago, our use of the bag has dropped considerably because of our more rigid adherence to proper indications. More than 70 per cent of all indications are for placenta previa, preeclampsia without pelvic disproportion, abruption of the placenta where vaginal delivery seems preferable to the abdominal route, primary inertia of the uterus and intrauterine fetal death. Of the 31 cases done for postmaturity, more than half were done in conjunction with a study being carried on. In contracted pelvis the bag was used an inconsiderable number of times. Obviously this is contraindicated except with a very small fetus.

Judging from our experience and from all the criteria available in this study, the No. 4 and No. 5 bags are the preferable sizes for the majority of cases. I still believe weights are valueless with rare exceptions, and are much more likely to do harm than to be of good. Most of the women in this series who had severe lacerations of the cervix were those who had weights used. They also increased the pain of lower segment distention, adding further to the patient's discomfort.

Reference to the morbidity table will show that approximately 25 per cent of our morbidities had no basis in the patient's course other than in her temperature readings and that a good many causes of fever, such as carbuncle of the thigh, bronchial asthma, etc., certainly could not be ascribed to bag induction. If we were to limit morbidity ascribable to the bag to cases showing endometrial or pelvic infection, the morbidity would be lowered to approximately 5 per cent.

Reifferscheid, W.: Local Treatment of Pruritus Vulvae With Follicle Hormone, *Monatsschr. f. Geburtsh. u. Gynäk.* 106: 287, 1937.

During 1924-1935 twenty-six patients with kraurosis vulvae were treated by means of radiation in the Würzburg clinic. Only one-third of these women were relieved. A noteworthy advance in the treatment of kraurosis was first suggested by Buschbeck and Seitz, namely, the use of follicle hormone. Subcutaneous injections yielded good results but Reifferscheid decided to apply follicle hormone locally in the form of a salve. This form of therapy proved to be most helpful and the author recommends its use for all cases of kraurosis vulvae. Even if it does not produce a cure it will result in great relief and improvement when used together with hypodermic injections.

J. P. GREENHILL.

A TEN-YEAR STUDY OF CESAREAN SECTION IN THE ST. LOUIS MATERNITY HOSPITAL

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IN 1933 a study of maternal deaths, in fifteen states which were included in the birth registration area, was made by the obstetric advisory committee of the United States Children's Bureau.¹ Regarding deaths following cesarean section it was commented. . . . "that there had been unwise selection of cases for operation, or of the types of operation, or both. . . ." In 1935, Stander² presenting statistics from the Woman's Clinic of the New York Hospital felt "the need to place this life-saving operation in its proper setting, both in regard to the indications and in respect to time and skill of operation, in order that its abuse may become legendary and the maternal mortality rate may be held within narrow minimal limits."

Numerous reports in the recent literature from private and teaching centers indicate a steadily increasing incidence of cesarean sections and a progressive decrease in maternal mortality.

This study encompasses the ten-year period from the opening of the St. Louis Maternity Hospital on Aug. 15, 1927 to Aug. 15, 1937. During this time there has been a change in incidence of operation, indications, type of operation, maternal mortality and maternal morbidity. Tables I to IX depict the experiences and results. The information has been analyzed in aggregate, in five-year periods and from the point of view of ward and private services.

INCIDENCE

Among 17,170 hospital deliveries during the ten-year period, 304 cesarean sections were performed (Table I).

Of these, 43 per cent were performed during the first five years and 57 per cent during the second period; this in spite of the fact that 56.2 per cent of all hospital deliveries occurred during the first five years.

The increase in frequency of operation from one in 88.5 to one in 51.5 deliveries on the ward service, and from one in 54.9 to one in 34.6 on the private service is significant. For the combined service, the recent incidence of 2.3 per cent, or one in 43.4 cases, indicates the progressive frequency with which cesarean section is being performed. Study of subsequent charts will explain the increase in incidence of operation.

Of the operations 85.2 per cent were primary and 14.8 per cent were repeat operations. The incidence of secondary operations was approximately the same on both ward and private cases.

TABLE I. INCIDENCE

| | WARD | PRIVATE | COMBINED |
|----------------------|----------|---------|----------|
| 1927-1932: | | | |
| Number of deliveries | 6,466 | 3,189 | 9,655 |
| Number of sections | 73 | 58 | 131 |
| Frequency | { 1.12% | 1.81% | 1.35% |
| | { 1-88.5 | 1-54.9 | 1-73.7 |
| 1932-1937: | | | |
| Number of deliveries | 4,635 | 2,880 | 7,515 |
| Number of sections | 90 | 83 | 173 |
| Frequency | { 1.93% | 2.88% | 2.30% |
| | { 1-51.5 | 1-34.6 | 1-43.4 |
| 1927-1937: | | | |
| Number of deliveries | 11,101 | 6,069 | 17,170 |
| Number of sections | 163 | 141 | 304 |
| Frequency | { 1.46% | 2.32% | 1.77% |
| | { 1-68.1 | 1-43.0 | 1-56.4 |

PARITY

Among the ward patients, during the first five years, 45 per cent of the patients operated upon were primiparas, and 38 per cent had had one or two previous pregnancies, a total of 83 per cent being para iii or less at the time of operation. Consistent with the increase in medical indication for operation and the high incidence of sterilization, we find that during the second five years, 24.7 per cent were primiparas and 28 per cent had one or two previous pregnancies, a total of 52.7 per cent gravida iii or less, and 47.3 per cent multiparas greater than iii at the time operated.

On the private service, during the first five years, 53.4 per cent of operations were performed in primiparas and 86.2 per cent on para iii or less. During the recent five-year period, again consistent with essentially the same general indications as previously, 61.7 per cent of the operations were performed on primiparas and 93.8 per cent on para iii or less at the time of operation.

INDICATIONS

Indications for cesarean section have been classified by ward and private services in each of the two five-year periods.

Apart from contracted pelvis as an indication the private and ward services differ greatly. On the private service is noted a greater diversity of percentage indication. An attempt is made, in this study, to list only the primary indications for operation. The difficulties offered in such a classification were more pronounced on the private service. Essentially, the indications for operation on private cases is the same in each five year group. The increase in frequency of operation cannot be attributed to a change in indications.

CONTRACTED PELVIS

Contracted pelvis is the most frequent indication for operation on both services, accounting for 40.5 per cent of all ward and 26.9 per cent of private operations, a combined incidence of 34.2 per cent.

MEDICAL INDICATIONS

During the first five years, 6.8 per cent of all ward operations were performed for medical reasons; during the second period 42.2 per cent were operated for similar reasons. This group of patients included cardiac, pulmonary and thyroid disease, essential hypertension, arthritis, patients with marked varicose veins, psychiatric and neurologic conditions. All of these patients were sterilized at the time of

operation. The medical condition is considered to be the fundamental indication for operation with the sterilization indication induced by the underlying medical state. It is this change in indication which is chiefly responsible for the increase in incidence of cesarean operations on the ward service.

TOXEMIA OF PREGNANCY

Toxemia of pregnancy is noted to be apparently less frequent as an indication for operation on both ward and private services in the latter five-year period. Of 24 ward sections, 10 were performed for eclampsia, 7 were for severe pre-eclampsia, and 7 for chronic nephritis. The pre-eclamptic patients were operated upon, with the toxemia as the only indication. In other cases a milder state of toxemia existed but the associated conditions such as large baby with danger of prolonged labor, desire for sterilization and tumors of the uterus were the primary indications for operation.

The apparently greater frequency of toxemia on ward than on private service warrants consideration. Although toxemias of pregnancy are noted more often on the wards, many of the severe cases are sent to the ward service by outside physicians, so that their consideration as ward patients is really not a true status.

Study of all toxemia patients in both periods indicates that approximately one-third fewer toxemia patients were observed during the latter five-year period. Thus one-half as many operations were performed on approximately two-thirds as many patients, less of a reduction in percentage incidence than study of Table II indicates.

TABLE II. INDICATIONS

| | 1927-1932 | | 1932-1937 | | TOTAL 1927-1937 | |
|---------------------|-----------|------|-----------|------|-----------------|------|
| | NO. CASES | % | NO. CASES | % | NO. CASES | % |
| <i>Private</i> | | | | | | |
| Contracted pelvis | 14 | 24.1 | 24 | 28.9 | 38 | 26.9 |
| Tumors | 6 | 10.4 | 9 | 10.8 | 15 | 10.6 |
| Medical indications | 5 | 8.6 | 7 | 8.4 | 12 | 8.5 |
| Postmaturity | 4 | 6.9 | 8 | 9.6 | 12 | 8.5 |
| Placenta previa | 5 | 8.6 | 6 | 7.3 | 11 | 7.8 |
| Toxemias | 6 | 10.4 | 3 | 3.6 | 9 | 6.4 |
| Previous section | 4 | 6.9 | 4 | 4.8 | 8 | 5.7 |
| Cervical dystocia | 1 | 1.7 | 6 | 7.3 | 7 | 4.9 |
| Previous plastic | 4 | 6.9 | 2 | 2.4 | 6 | 4.2 |
| Miscellaneous | 9 | 15.6 | 14 | 16.8 | 23 | 16.4 |
| <i>Ward</i> | | | | | | |
| Contracted pelvis | 33 | 45.2 | 33 | 36.6 | 66 | 40.5 |
| Medical indications | 5 | 6.8 | 38 | 42.2 | 43 | 26.4 |
| Toxemias | 16 | 21.9 | 8 | 8.9 | 24 | 14.8 |
| Tumors | 5 | 6.8 | 3 | 3.4 | 8 | 5.0 |
| Postmaturity | 4 | 5.5 | 1 | 1.1 | 5 | 3.1 |
| Cervical dystocia | 1 | 1.4 | 3 | 3.4 | 4 | 2.5 |
| Placenta previa | 2 | 2.8 | 1 | 1.1 | 3 | 1.3 |
| Miscellaneous | 7 | 9.6 | 3 | 3.3 | 10 | 6.3 |

PLACENTA PREVIA

Eleven private patients were operated because of placenta previa and only three on the ward service.

In previous years a difference in handling such cases existed on the two services. In addition to blood transfusions and general supportive measures, the ward cases were treated formerly by packing properly inserted. More recently partial and central placenta previa with viable babies are treated by cesarean section.

The incidence of all placenta previa cases is the same among ward and private cases. A study of these cases is now in progress.

The average weight of babies of ward placenta previa cases is 2,550 gm. as compared with 3,240 gm. on the private service. This would indicate that the private patient on the average carries her baby nearer to term.

With cesarean section reserved for those cases where there is reasonable expectancy of obtaining a good living baby, the explanation of the greater number of private patients sectioned for placenta previa is obtained.

TUMORS

Seven of 8 ward patients operated upon for tumors were treated by hysterectomy. One tumor was an impacted ovarian cyst.

Eight of 15 private patients were sterilized, the remaining patients treated by myomectomy following cesarean section.

POSTMATURITY

Among the ward cases these babies weighed between 4,000 and 5,100 gm. In every case, also, another indication for operation existed, mild pre-eclampsia, borderline pelvis or breech presentation.

On the private service the greater frequency of this indication is noted. Five of 12 operations were performed with postmaturity as the only indication. Such babies weighed between 3,800 and 6,200 gm. Three were performed on elderly primiparas with myomatous uteri or contracted pelvis. One each was associated with inertia, contracted pelvis, breech, and heart disease.

MISCELLANEOUS INDICATIONS

These indications included antepartum hemorrhage, contraction ring, elderly primiparas with breech, elderly primiparas with no complications, abruptio placentae, previous section with morbidity, previous section with peritonitis, previous section with breech, dwarfism, marked vaginal condylomas, aneurysm, marked umbilical hernia, and breech with fetal embarrassment.

TYPE OF OPERATION

Prior to 1927, practically all operations were of the classical type. From 1927 to 1932 the low cervical operation with longitudinal incision in the lower uterine segment was favored equally with the classical operation in the ward service. On the private service the classical operation was performed in 86.2 per cent of cases as compared with 13.8 per cent of the low cervical type; with a combined incidence of classical operation in 64.9 per cent of cases.

Since 1932, the low cervical operation with a transverse incision in the lower uterine segment, as advocated by Phaneuf,³ has become popular. On the private service the classical operation is still performed in 65 per cent of cases, but on the ward service 73.3 per cent of cases are of the low cervical type and 55.6 per cent of the ward operations are with the transverse incision in the lower segment.

The transverse low cervical operation is of especial value in those cases where hysterectomy is to be performed. The pedicles need but be clamped and cut to the level of the transverse incision, and the uterus is then removed readily by carrying the incision around posteriorly. The ease with which hysterectomy can be performed after the transverse low cervical incision is to be emphasized.

During the first five-year period, hysterectomy was performed after classical operation in 14 of 17 cases. During the second five-year period, 18 of 34 hysterectomies were performed after the transverse low cervical operation, 10 after classical and 5 after the longitudinal low cervical operations.

The longitudinal low cervical operation has never been very popular on the private service. During the ten-year period only 18 of 141 operations (12.7 per cent) on the private service were of the longitudinal low cervical type; whereas 19 transverse low flap operations (13.4 per cent) of the entire private service have been performed in the past four years alone.

MATERNAL MORTALITY

Table III shows the maternal mortality during the two five-year periods. Only one maternal death occurred in 173 operations performed during the past five years. The factors to be considered in this lowered mortality rate include the increase in number of elective operations, preparation of the patient for operation with antiseptic vaginal instillations and possibly the choice of type of operation.

TABLE III. MATERNAL MORTALITY

(Combined Service)

| 5-YEAR PERIODS | DEATHS | OPERATIONS | MORTALITY PER CENT |
|--------------------------------|--------|------------|-----------------------|
| Aug. 15, 1927 to Aug. 15, 1932 | 8 | 131 | 6.10 |
| Aug. 15, 1932 to Aug. 15, 1937 | 1 | 173 | 0.57 |
| Total | 9 | 304 | 2.96 |

Table IV presents a protocol of the maternal deaths. Seven deaths occurred in elective cases and 2 after the onset of labor. Four of the 9 deaths (44 per cent) were attributable to sepsis. Two deaths in 1929 occurred during a mild epidemic of staphylococcus infections.

TABLE IV. MATERNAL DEATHS; 1927-1937

| |
|---|
| 1. 4668. Ward. Previous section. Flat rachitic pelvis. Elective. Low cervical. Pneumonia. |
| 2. 12940. Ward. Flat rachitic pelvis. Long labor on outside. Low cervical. Septicemia. |
| 3. 13492. Ward. Eclampsia without coma or convulsions. Elective. Classical. |
| 4. 13450. Private. Decompensated cardiac. Elective. Classical. |
| 5. 5915. Private. Inertia. Ruptured membranes 3 days. Classical. <i>Staphylococcus albus</i> peritonitis. |
| 6. 9155. Ward. Contracted pelvis. Eclampsia. Elective. Low cervical. Adynamic ileus. |
| 7. 2049. Ward. Incarcerated myoma. Elective. Porro. Hemorrhage from pedicle. |
| 8. 6148. Private. Toxemia. Elective. Low cervical. <i>Staphylococcus albus</i> . |
| 9. 18722. Ward. Nephritis. Heart disease. Elective. Low cervical + hysterectomy. 4 hour postoperative shock. Cardiac. |

The deaths with relation to the indication for operation are reviewed in Table V.

Table VI demonstrates that there has been no maternal death with the performance of the transverse low cervical operation. Explanation of the high mortality with the longitudinal low cervical operation lies in Table IV.

The maternal mortality for the entire series is 2.96 per cent. The mortality for the last five years is 0.57 per cent.

DURATION OF LABOR

On the ward service during the first five years, 60.5 per cent of cesarean sections were performed as elective operations with no labor, 18.3 per cent in labor 0 to 12 hours, 11.2 per cent in labor 12 to 24 hours, and 10 per cent in labor more than 24 hours. During the second period of time, 82 per cent of the ward operations were elective, 10 per cent in labor 0 to 12 hours, 4.5 per cent in labor 12 to 24 hours, and 3.5 per cent in labor more than 24 hours. More frequently, recently, possible cesarean section patients are hospitalized, prepared, and operated upon sooner than formerly.

TABLE V. MATERNAL MORTALITY WITH RELATION TO INDICATION FOR OPERATION

| INDICATION | NO. OF OPERATIONS | DEATHS | PER CENT MORTALITY |
|---------------------|-------------------|--------|--------------------|
| Contracted pelvis | 104 | 3 | 2.88 |
| Toxemia | 33 | 2 | 6.06 |
| Medical indications | 55 | 2 | 3.63 |
| Tumors | 23 | 1 | 4.34 |
| Miscellaneous | | 1 | |

TABLE VI. MATERNAL MORTALITY (10 YEARS)

| TYPE OF OPERATION | WARD | | | PRIVATE | | | COMBINED | | |
|-------------------|--------|-------------------|---------|---------|-------------------|---------|----------|-------------------|---------|
| | DEATHS | NO. OF OPERATIONS | MORT. % | DEATHS | NO. OF OPERATIONS | MORT. % | DEATHS | NO. OF OPERATIONS | MORT. % |
| Classical | 2 | 58 | 3.44 | 2 | 104 | 1.92 | 4 | 162 | 2.46 |
| Longitudinal | 4 | 53 | 7.54 | 1 | 18 | 5.55 | 5 | 71 | 7.04 |
| low cervical | | | | | | | | | |
| Transverse | 0 | 51 | 0 | 0 | 19 | 0 | 0 | 70 | 0 |
| low cervical | | | | | | | | | |
| Unclassified | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Total | 6 | 163 | 3.68 | 3 | 141 | 2.12 | 9 | 304 | 2.96 |

On the private service the duration of labor was essentially the same in each period. Eighty-two and four-tenths per cent were elective operations, 12.2 per cent were in labor 0 to 12 hours, and 5.2 per cent were in labor more than 12 hours.

PREPARATION OF PATIENT

The procedure of choice with patients who are to have elective cesarean sections or who are considered as possible candidates for this operation is as follows: The patients are hospitalized several days before contemplated operation and receive a complete medical work-up. Vaginal instillations of 8 c.c. of 1 per cent neutral acriflavine hydrochloride in glycerin are administered twice a day for a few days prior to operation. When in labor and the patient is being subjected to a test of labor such instillations are administered every eight hours.

As noted above in this discussion 92 per cent of the ward patients and 94.6 per cent of the private patients presented labors from 0 to not more than 12 hours. Table IV also demonstrates that 2 of the 9 deaths were associated with prolonged labor or long ruptured membranes.

It is felt, from the bacteriologic studies made from intrauterine cultures taken at the time of operation, that a definite safety measure exists in the use of the acriflavine instillations. More adequate tests of labor can be allowed under such procedure.

The bacteriologic studies performed in this series with analyses regarding duration of labor and maternal morbidity will be the subject of a separate communication by T. K. Brown of this department.

STERILIZATION

Table VII shows that 49.1 per cent of ward operations and 31.2 per cent of private cases were accompanied by a sterilization operation.

The high incidence of medical indications for operation here explains the major portion of the general increase in cesarean operations on the ward service during the period of time of this study.

Table VIII shows the various operations performed for sterilization purposes. Hysterectomy is the method of choice in this series, and in recent years performed most frequently after the transverse low cervical type of operation.

TABLE VII. STERILIZATION

| | 1927-1932 | 1932-1937 | TOTAL | PER CENT |
|-------------------------------------|-----------|-----------|-------|----------|
| <i>Private Patients</i> | | | | |
| Number of sections | 58 | 83 | 141 | |
| Number of sterilizations | 18 | 27 | 45 | 31.2 |
| <i>Indications:</i> | | | | |
| Contr. pelvis with previous section | 5 | 3 | 8 | |
| Contracted pelvis | 1 | 1 | 2 | |
| Tumors | 3 | 5 | 8 | |
| Previous plastic | 3 | 2 | 5 | |
| Medical indications | 2 | 3 | 5 | |
| Placenta previa | 2 | 2 | 4 | |
| Previous section | 1 | 3 | 4 | |
| Sterilization | 0 | 3 | 3 | |
| Cervical dystocia | 0 | 2 | 2 | |
| Toxemia | 1 | 1 | 2 | |
| Unclassified | 0 | 2 | 2 | |
| <i>Ward Patients</i> | | | | |
| Number of sections | 73 | 90 | 163 | |
| Number of sterilizations | 25 | 55 | 80 | 49.1 |
| <i>Indications:</i> | | | | |
| Medical indications | 5 | 38 | 43 | |
| Contr. pelvis with previous section | 3 | 5 | 8 | |
| Contracted pelvis | 5 | 5 | 10 | |
| Tumors | 5 | 2 | 7 | |
| Toxemia, nephritis | 2 | 2 | 4 | |
| Previous section | 1 | 2 | 3 | |
| Placenta previa | 1 | 1 | 2 | |
| Previous plastic | 1 | 0 | 1 | |
| Postmaturity with manipulation | 1 | 0 | 1 | |
| Stenosis cervix | 1 | 0 | 1 | |

TABLE VIII. STERILIZATION: TYPE OF OPERATION

| OPERATION | HYSTERECTOMY | TUBAL RESECTION |
|---------------------------|--------------|-----------------|
| <i>Private Service</i> | | |
| Classical | 28 | 12 |
| Longitudinal low cervical | 1 | 0 |
| Transverse low cervical | 2 | 3 |
| | 31 | 15 |
| <i>Ward Service</i> | | |
| Classical | 24 | 12 |
| Longitudinal low cervical | 9 | 3 |
| Transverse low cervical | 18 | 12 |
| Unclassified | 1 | 0 |
| | 52 | 27 |

FETAL MORTALITY

This is demonstrated in Table IX on ward and private services in each five-year period.

These statistics are not corrected for abnormality (hydrocephalus), prematurity, or operations performed solely in the interest of the mother without regard to the size of the baby. The explanation of the change in fetal mortality statistics is obtained by noting the indication for operation in the respective cases in which fetal mortality was observed.

Of the 11 fetal deaths in the first five-year period on the ward service, 5 were associated with long labors, 3, all prematures, were noted in nephritic toxemias, and

1 in an eclamptic mother. Thus 9 of the 11 deaths were associated with maternal conditions which today are modified indications for cesarean section.

TABLE IX. FETAL MORTALITY

| | NO. DELIVERIES | NO. DEATHS | PER CENT |
|------------|----------------|------------|----------|
| 1927-1932: | | | |
| Private | 58 | 4 | 6.9 |
| Ward | 73 | 11 | 15.0 |
| Combined | 131 | 15 | 11.4 |
| 1932-1937: | | | |
| Private | 83 | 4 | 4.8 |
| Ward | 90 | 6 | 6.6 |
| Combined | 173 | 10 | 5.8 |

SUMMARY

1. The incidence of cesarean section has increased from 1:73.7 (1927-1932) to 1:43.4 (1932-1937).

2. The explanation of the increase in incidence on the ward service lies in the increase in number of operations performed for "medical" conditions rather than purely obstetric reasons.

3. The low segment operation is preferred on the ward service. In recent years the transverse incision in the lower segment has been the operation of choice.

4. The maternal mortality for ten years is 2.9 per cent. The maternal mortality for the past five years is 0.57 per cent.

5. Forty-four per cent of the maternal deaths were attributed to sepsis.

6. The use of one per cent acriflavine (neutral) hydrochloride in glycerin as a vaginal instillation before operation is recommended.

7. The uncorrected fetal mortality for ten years is 8.2 per cent; for the last five years, 5.8 per cent.

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Rodecurt: Late Results in Treatment of Pruritus Vulvae With Progynon,
 Zentralbl. f. Gynäk. **61**: 2159, 1937.

In 1936 Rodecurt published his results in the treatment of pruritus vulvae by means of estrogenic substance. He concluded that the effects are too uncertain, that recurrences and bleeding are too frequent and difficult to avoid, to accept this expensive form of treatment as the method of choice. He now reconsiders this problem because he had occasion to reexamine four patients. All have been relieved of their disagreeable symptoms during the 12 to 22 months which have elapsed. Hence the author is now of the opinion that estrin therapy for pruritus vulvae is worth while.

J. P. GREENHILL.

A COMPARISON OF THE END-RESULTS OF TREATMENT OF ENDOCERVICITIS BY ELECTROPHYSICAL METHODS: CAUTERY, COAGULATION, AND CONIZATION

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MANY therapeutic methods for chronic inflammation of the endocervix, including both chemical and physical agents, have been advocated and are in use at the present time. Those which utilize the electric cautery, the high frequency current adjusted to coagulate tissue, or the high frequency current regulated to excise portions of tissue, are probably the most popular. The technics for cautery,¹ coagulation,² and coning,³ of the cervix have been adequately described. Technically, the simplest of these procedures is coagulation, then cauterization, and the most difficult is conization, or coring of the cervical mucosa; however, all of these methods are easily carried out by the experienced gynecologist.

This investigation was undertaken to make a comparative estimate of the end-results in patients treated by these three methods. One hundred and fifty cases, 50 each treated with cautery, coagulation, and coning, were used in this study. Tables I to III indicate that the patients in every group presented similar symptoms and physical findings.

TABLE I. SOCIAL GROUP

| | NUMBER OF CASES | AVERAGE AGE | M. S. | | CHILDREN | | |
|---------------|--------------------|----------------|-------|---|----------|-----|------|
| | | | | | NONE | ONE | MORE |
| Cauterization | 50 | 30 | 46 | 4 | 7 | 11 | 32 |
| Coagulation | 50 | 31 | 46 | 4 | 13 | 12 | 25 |
| Conization | 50 | 33 | 47 | 3 | 18 | 8 | 24 |

TABLE II. SYMPTOMS

| | MENSTRUATION | | DISCHARGE | | | PAIN | | |
|---------------|--------------|--------|-----------|---------------|--------------|------|------|----------------|
| | REG. | IRREG. | SLIGHT | MOD- ERATE | PRO- FUSE | NONE | BACK | LOWER QUAD. |
| Cauterization | 40 | 10 | 22 | 11 | 17 | 14 | 19 | 23 |
| Coagulation | 37 | 13 | 17 | 10 | 23 | 15 | 21 | 21 |
| Conization | 42 | 8 | 16 | 11 | 23 | 15 | 19 | 19 |

TABLE III. PHYSICAL EXAMINATION

| | EROSION | | | CYSTS | | | PARAMETRIUM | |
|---------------|---------|--------|--------|-------|-----|------|-------------|---------|
| | NONE | SLIGHT | MARKED | NONE | FEW | MANY | POST. | LATERAL |
| Cauterization | 17 | 10 | 23 | 25 | 3 | 22 | 27 | 6 |
| Coagulation | 14 | 15 | 21 | 36 | 5 | 9 | 27 | 3 |
| Conization | 23 | 11 | 16 | 35 | 6 | 9 | 26 | 4 |

The similarity of the three groups of cases permits a fair comparison. In evaluating the results, a patient was considered cured only when all symptoms had disappeared and the cervix was restored to normal. Such determinations necessitated prolonged follow-up and treatment, which in some cases extended over two years. In the group treated by coagulation such prolonged observations and treatment were carried out in all 50 patients. In the groups treated by cauterization and conization this was possible in only 44 patients. The other 6 in each group failed to reappear soon after the treatment was given, and could not be located thereafter.

DURATION FOR CURE

The time required to bring about a cure in each of the groups is indicated in Table IV. In order to bring about a cure in some patients, the same or one of the other technical procedures had to be repeated. Existing Nabothian cysts and cysts formed at a subsequent time required treatment. In every case, regardless of which modality was originally used, Nabothian cysts were destroyed by actual cautery.

TABLE IV. TIME REQUIRED FOR CURE

| | CAUTERY | COAGULATION | CONING |
|----------------------|---------|-------------|---------|
| Average | 4 mo. | 7 mo. | 7.3 mo. |
| Shortest | 2 mo. | 2 mo. | 2 mo. |
| Longest | 12 mo. | 31 mo. | 19 mo. |
| Number in 2 mo. | 19 | 10 | 5 |
| Number in 3 or 4 mo. | 13 | 15 | 10 |

In several of the cases developing cysts subsequent to the original treatment, repeated groups of cysts appeared at varying intervals. The number of patients requiring such additional treatment and the total number of times instituted, in the entire groups of patients, are shown in Table V.

TABLE V. ADDITIONAL TREATMENT

| | REPEAT | | CYSTS CAUTERIZED | |
|---------------|--------|--------------------------|------------------|-----------------|
| | SAME | OTHER | PREEXISTING | NEWLY DEVELOPED |
| Cauterization | 0 | 1 (Cone) | 22 cases | 5 (4 cases) |
| Coagulation | 2 | 4 (2 Caut.) (2 Cone) | 9 cases | 14 (9 cases) |
| Conization | 2 | 3 (1 Caut.) (2 Coag.) | 11 cases | 18 (17 cases) |

COMPLICATIONS

In no patient following cauterization in this series was any complication noted. In one patient treated by coagulation, bleeding from the cervical canal occurred after the slough had separated, but was easily controlled. In 6 patients following coagulation, stenosis of the cervical canal occurred, but in no case was the atresia absolute, and gradual

dilatation promptly corrected the stenosis. In 4 patients following coagulation and in 3 after conization, a marked tuboovarian inflammation was excited. These patients were treated by rest in bed and given the usual treatment for acute pelvic inflammation. In 6 patients after coagulation of the cervix, a temporary amenorrhea followed, lasting from three to fourteen months. In one patient after coagulation and in one following conization, the next menstrual flow was unusually profuse.

TABLE VI. COMPLICATIONS

| | CERVIX | | INFLAMMATION TUBES AND OVARIES | MENSTRUATION | |
|---------------|----------|----------|--------------------------------------|-----------------|------------------|
| | BLEEDING | STENOSIS | | AMENOR- RHEA | MENOR- RHAGIA |
| Cauterization | 0 | 0 | 0 | 0 | 0 |
| Coagulation | 1 | 6 | 4 | 6 | 1 |
| Conization | 0 | 0 | 3 | 0 | 1 |

TABLE VII. COMPARATIVE RATING

| | CAUTERY | CONING | COAGULATION |
|-------------------------|---------|---------|-------------|
| Time for cure | 1 | 3 | 2 |
| Repetition of treatment | 1 | 2 | 3 |
| New cyst formation | 1 | 3 | 2 |
| Complications | | | |
| Stenosis | 1 | 1 | 2 |
| Inflammation | 1 | 2 | 3 |
| Menstruation | 1 | 2 | 3 |
| Final rating | 1 | 2.2 (2) | 2.5 (3) |

COMMENT

The pathology present in this series of cases demonstrated that an inflammation of the cervix is seldom limited to the mucosa; it more commonly involves all the structures in the cervix and often extends into the lymphatics of the parametrial tissue. The glandular tubules in the cervical mucosa are occluded and filled with inflammatory exudate. The modalities used primarily destroy the cervical mucosa, either by cauterization, coagulation, or excision of tissue, but neither Nabothian cysts nor the lymphatic involvements are immediately affected, and it is therefore necessary to attack them independently. The cautery is best adapted to the treatment of Nabothian cysts, as well as for a cervical erosion when an erosion requires special treatment. The appearance of the cervix a few days after either cauterization, coagulation, or conization is practically the same, and the subsequent progress and healing after all three methods is almost identical. From the number of patients requiring destruction of newly formed Nabothian cysts during the course of observation after the first treatment, especially noticeable in those cases coned and coagulated, it seems that these glands are not completely removed with the mucosa. This may be due to a failure to remove enough tissue, or to the deep penetration of these glands. In either case, the healing of the mucosa in the canal forms an impenetrable roof, which sooner or later results in the enlargement of these glands, distended with a reaccumulation of inflammatory exudate. The fre-

quency of partial cervical stenosis following coagulation may be due to an individual variation in the tissue resistance to the penetration of the current. This would influence the depth of coagulation produced with a standard amount of current. Too deep coagulation will cause excess connective tissue formation, with subsequent contraction and stenosis. The reason for the amenorrhea produced in some patients following coagulation is not clear.

SUMMARY

One hundred and fifty cases of cervical inflammation were treated by cauterization, coagulation, or conization of the cervical canal.

One hundred and thirty-eight cases were followed to a point of complete cure: that is, freedom from symptoms and eradication of pelvic pathology. Fifty were in the group treated by coagulation and 44 each in the groups treated by cauterization and conization.

The average length of time required to cure patients treated by cauterization was four months. Nineteen were cured in two months and 13 in three or four months.

The average length of time required to cure patients treated by coagulation was seven months. Ten were cured in two months and 15 in three or four months.

The average length of time required to cure patients treated by conization was 7.3 months. Five were cured in two months and 10 in three or four months.

Repetition of the same or one of the other methods was necessary in one case originally cauterized, in 5 cases originally coned, and in 6 cases originally coagulated.

Newly formed cysts developed and were treated in 4 patients originally cauterized, in 9 patients originally coagulated and in 17 patients originally coned.

Moderate stenosis of the cervical canal occurred in 6 patients treated by coagulation.

Acute inflammation of the tubes and ovaries developed in 4 patients treated by coagulation, and in 3 treated by conization.

Six patients treated by coagulation had subsequent periods of amenorrhea lasting from three to fourteen months.

CONCLUSION

From the discussion and summary, it is evident that all three methods are satisfactory for removing the diseased cervical mucosa.

The patients treated by cauterization are cured more quickly and with fewer complications than those treated by the other two methods.

Nabothian cysts and cervical erosions are best treated by cauterization.

The cautery is superior to the other two electrophysical methods for treating chronic cervical inflammations.

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THE EFFECT OF SODIUM LACTATE IN RAISING THE CO₂ COMBINING POWER IN THE TOXEMIAS OF PREGNANCY

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IN NORMAL pregnancy, there is a depletion in the alkali reserve, as shown by the lowered CO₂ combining power. In the more severe toxemias, this alkali deficit is often aggravated, and tends to become uncompensated. That is, the pH of the blood, which has been very nearly constant, now is likely to fall.

Stander, Eastman and Harrison,¹ and Stander and Eastman² found that in eclampsia the blood pH falls as low as 7.0. This degree of acidity would, of itself, be fatal if long maintained. Furthermore, the authors cited have suggested that the high fetal mortality in eclampsia may be caused by the acidosis. These workers have shown that the marked acidosis of eclampsia seems to follow the convulsions, and if these be controlled, the patient can restore the blood pH to normal or nearly so. The explanation of the fall and subsequent rise in the blood pH and CO₂ combining power lies in the accumulation of organic acids, chiefly lactic acid resulting from muscular contraction, and ketone and other bodies. These acids are neutralized by the alkali reserve, giving their sodium salts. Thus the CO₂ combining power is diminished. After the convulsion, the sodium lactate is oxidized, and because of its ketolytic activity, so are ketone bodies. In this way sodium is again set free and is promptly bound as bicarbonate. The kidney, by excreting buffers and ammonia, releases still more sodium. Thus the alkali reserve rises. Meanwhile some of the sodium salts of these organic acids will be lost in the urine and deplete still further the blood alkali. Progressively then, the alkali deficit is aggravated, buffering power is lost, and the body is less able to combat the metabolic acids ordinarily and extraordinarily produced.

In the severe nonconvulsive toxemias, the CO₂ combining power often falls. Here, while the accumulation of organic acids is not so acute as in convulsions, the alkali depletion is progressive and the patient may be unable to regain the normal level of alkali reserve. If convulsions should occur, the resulting acidosis might be overwhelming.

In order to protect the patient from acidosis, an important feature in the treatment of toxemia of pregnancy has been to maintain or raise the CO₂ combining power. Glucose, with or without insulin, is widely used since its oxidation is ketolytic.

In the face of the primary alkali deficit, which has a tendency toward aggravation, glucose therapy may not be sufficient to raise or even maintain the alkali reserve.

Following this line of thought, Wilson³ treated 14 patients who had severe cases of toxemia with intravenous sodium bicarbonate. All showed favorable reactions, both clinically and in the increased CO_2 combining power of the plasma. Stander, Eastman and Harrison concluded from their detailed study of the acid-base equilibrium in eclampsia that glucose is inadequate, and recommend intravenous bicarbonate.

Since sodium lactate has several advantages over sodium bicarbonate, its usefulness in toxemia of pregnancy is suggested. These advantages of the lactate are:

1. Sodium lactate is easily sterilized, while bicarbonate is not. The latter decomposes to the caustic carbonate when heated above 80°C .
2. Sodium lactate releases sodium only as it is metabolized, thus changing the blood alkali more slowly and uniformly than would infused bicarbonate.
3. Sodium lactate is ketolytic, a molar solution being equivalent to 18 per cent glucose.
4. This treatment utilizes a normal physiologic mechanism, since large quantities of sodium lactate are found in the blood following exercise, and are metabolized.

In 1924, Haldane⁴ suggested the use of the sodium salts of acetic, citric, or other oxidizable organic acids as a means of raising the alkali reserve. The oxidation of the organic ion leaves sodium to be combined as bicarbonate.

Abramson and Eggleton⁵ studied in detail the utilization of infused sodium *r*-lactate. They showed that the metabolism of lactate was paralleled by an increase in the CO_2 of the blood.

Hartmann and Senn⁶ report the successful and satisfactory use of sodium *r*-lactate infusions in overcoming the acidosis of nephritis, diabetes, and dehydration. They believe that 60 per cent of the utilized lactate is oxidized at once, while 40 per cent forms liver glycogen. Abramson, Eggleton and Eggleton⁷ could not demonstrate the deposition of liver glycogen in the dog.

Hartmann and Senn⁶ have modified a formula derived by Palmer and Van Slyke,⁸ by which they calculate the dose of lactate required to produce a desired increment in the CO_2 combining power. It is assumed that 67 per cent of the body weight is water, and that the BHCO_3 is evenly distributed in that water and equal to the plasma level. One milliliter of molar sodium lactate, completely metabolized, will yield 1 ml. of molar sodium bicarbonate which will be equivalent to 22.4 ml. of CO_2 per liter. Therefore the expected increase in CO_2 , after sodium lactate, is:

$$\text{Increase (in volumes per cent)} = \frac{2.24 \times \text{ml. molar Na lactate}}{\text{Body wt. in kg.} \times 0.67}$$

Simplifying and transposing, this becomes:

$$(\text{Dose ml. of Na lactate} = 0.3 (\text{body wt., kg}) \times (\text{Vol. per cent desired increase in } \text{CO}_2).$$

For example, a patient weighing 60 kg. has a CO_2 combining power of 26. It is desired to raise the CO_2 to 40, *i.e.* by 14 volumes per cent.

$$\text{Dose (in ml. of molar lactate)} = 0.3 \times 60 \times 14 = 252.$$

In the example cited, if 252 ml. of molar lactate be given, the CO_2 should rise to 40. This expected level will hereafter be referred to as the "calculated CO_2 ."

In the present study, the molar lactate was diluted with distilled water in proportions up to 1:5, which is isotonic, and given by venoclysis. The dilution depended upon the amount of fluid which the patient was considered to need.

The CO_2 combining power of the plasma was determined in duplicate by the method of Van Slyke and Cullen,⁹ using the manometric apparatus. The blood was taken either without stasis or with minimal stasis. It was not drawn anaerobically, but was in the centrifuge within five minutes.

RESULTS AND DISCUSSION

In Table I are summarized all of the results of sodium lactate therapy thus far observed. The greatest discrepancy between the measured and calculated CO_2 combining powers is plus 7 volumes per cent in a patient who received 80 gm. of glucose just before, during, and after the lactate infusion. The mean difference for the whole group is plus 1.3 volumes per cent. Omitting patients who were given glucose, the greatest discrepancy is plus 5, the next minus 3; the mean difference between calculated and measured CO_2 is plus 0.5 volumes per cent.

It will be observed, in the last column of the table, that a rise in the level of blood uric acid is usually seen after sodium lactate is given intravenously. In view of the importance which has been attached to the blood uric acid as an indicator of liver function in the toxemias of pregnancy, this finding requires some explanation. Quick¹⁰ has shown that sodium lactate inhibits the renal excretion of uric acid. This would result in an increase in the blood level without necessarily meaning any

TABLE I. THE EFFECT OF SODIUM LACTATE IN RAISING THE CO_2 COMBINING POWER IN TOXEMIA OF PREGNANCY

| DIAGNOSIS | CO_2 C.P. BEFORE VOL. % | CO_2 C.P. AFTER VOL. % | CO_2 C.P. CALCULATED VOL. % | ERROR VOL. % | GLUCOSE GRAMS | URIC ACID CHANGE MG. % |
|---|--|---------------------------------------|--|-----------------|------------------|------------------------------|
| Eclampsia | 44 | 54 | 54 | 0 | 0 | +1.4 |
| Eclampsia (?) | 12 | 42 | 36 | +6 | 75 | +9.5 |
| Pre-eclampsia | 30 | 48 | 46 | +2 | 0 | -1.2 |
| Pre-eclampsia | 32 | 39 | 38 | +1 | 0 | +1.4 |
| Pre-eclampsia | 38 | 57 | 55 | +2 | 0 | +1.1 |
| Pre-eclampsia | 32 | 51 | 48 | +3 | 50 | -2.1 |
| Pre-eclampsia | 36 | 61 | 54 | +7 | 80 | +1.9 |
| Pre-eclampsia | 35 | 51 | 51 | 0 | 0 | - |
| Pre-eclampsia | 36 | 44 | 47 | -3 | 0 | 0 |
| Pre-eclampsia | 37 | 53 | 48 | +5 | 0 | - |
| Abruptio, oliguria | 32 | 48 | 45 | +3 | 350 | +0.6 |
| Abruptio, anuria, ure- mia, death | 12 | 27 | 22 | +5 | 50 | Trans- fusion |
| | 27 | 36 | 41 | -5 | 0 | |
| | 32 | 38 | 40 | -2 | 0 | |
| | 38 | 44 | 42 | +2 | 30 | |
| Terminal uremia | 32 | 63 | 62 | +1 | 0 | |
| Pyelitis | 36 | 50 | 49 | +1 | 0 | +0.2 |
| Hydronephrosis | 38 | 51 | 49 | +2 | 0 | |
| Hydronephrosis | 33 | 50 | 48 | +2 | 0 | +0.1 |
| Average | | | | +1.3 | | +1.4 |

failure on the part of the liver to destroy its quota of uric acid arising from the metabolic processes. Fortunately, there is another consideration which militates against the interpretation that the lactate may be inhibiting an already impaired liver. In two of the patients, the icteric index was elevated to about 15. Following the lactate infusion, the index fell in both of these. It might be pointed out again that 40 per cent of the lactate is thought to form liver glycogen, and thus has a favorable effect upon that organ. This deposition of glycogen is one of the ends in view when glucose is given in treating toxemia. Furthermore, Hartmann and Senn⁶ have shown that patients with marked liver damage utilize the lactate about as well as normals.

The close agreement between the expected and actual effect of the lactate upon the CO_2 indicates that the lactate is practically all metabolized. This fact partially answers what we had considered as a possible objection to the use of sodium lactate in toxemia therapy. Stander and

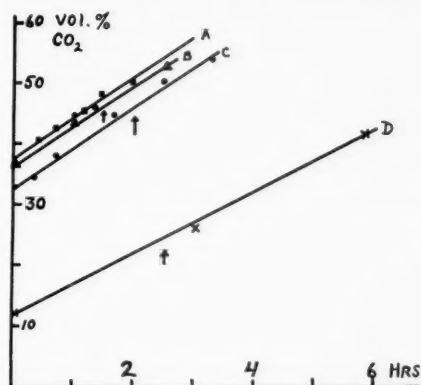


Chart 1.—The rate of increase in CO_2 combining power of the plasma after intravenous injections of sodium lactate. A and C (■ and ●) are normal subjects. B (▲) pre-eclamptic patient. D (×) eclamptic patient.

Radelet¹¹ observed that in toxemias of all groups the blood lactate is elevated. This was interpreted as a possible indication of an upset in carbohydrate metabolism, probably concerned with the synthesis of glycogen from lactate.

Hartmann and Senn⁶ found in diabetes, nephritis and dehydration that the measured CO_2 usually fell short of the expected level. In some of their cases, as much as 18 per cent of the infused lactate was lost in the urine, and was thus not available for metabolism. Perhaps the oliguria present in most of our toxemia patients limited the renal excretion of lactate, and is responsible for the apparently more complete utilization.

The rate of increase in CO_2 combining power, which is proportional to the rate of metabolism of the lactate, was followed in some cases. In Chart 1 is shown the rise in CO_2 combining power in two "normals" in comparison with two toxemia patients. The "normals" were cases of hydronephrosis whose CO_2 combining powers had been driven down by

ammonium chloride given in treating the supposed pyelitis. Since the metabolism of sodium lactate by normal subjects has been investigated in detail by authors cited above, further controls were not used. Of the toxemia patients, one was a pre-eclamptic; the other was a severe eclamptic whose CO_2 was increased from 12 to 42 volumes per cent by lactate, which also cleared up a four-plus ketonuria.

The lines describing the increase in CO_2 combining power seem to be straight. This would indicate that the rate of metabolism of the infused lactate is nearly constant. Since the lines appear to be straight over the period of the infusion, it follows that the lactate is metabolized at a rate independent of its concentration in the blood, at the levels with which we are concerned.

Since the lines shown on the graph are nearly parallel, it appears that the toxemia patients utilized the lactate as efficiently as did the normal subjects. This fact gives another answer to the possible objection mentioned above; i.e., that in toxemia the blood lactate is already elevated.

In at least six cases previous treatment with glucose, with or without insulin, had either been ineffective or had exerted its maximal effect in raising the CO_2 combining power. All of these patients showed the predicted rises in CO_2 when given lactate.

Usually the level of CO_2 established by the lactate was stable as shown by subsequent determinations of the CO_2 over a period of days.

Several of the patients had an increase in temperature and pulse rate and a hyperemia of the skin which appeared during the infusion and disappeared within four to six hours. The average dose of lactate given would result in the production of about 2 calories per kilogram per hour. This is about twice the basal metabolic rate for women of this group, and probably accounts for the temperature and pulse elevation.

The number of ante-partum patients who received lactate therapy for acidosis is much too small for any evaluation of the effect of the treatment in reducing fetal mortality. In the 5 patients carrying viable and living fetuses, all had living babies. In two other ante-partum cases, the fetus had died in utero before the lactate was given, and in one other the mother died undelivered in the fifth month of pregnancy.

SUMMARY

Sodium lactate has several advantages over sodium bicarbonate in the treatment of acidosis.

A series of patients with toxemia of pregnancy has been treated with sodium lactate intravenously. In all cases the CO_2 combining power was raised by amounts which had been closely predicted from the dose of lactate given.

The sodium lactate seems to be almost completely metabolized by the toxemic patient. This metabolism seems to be as efficient as in normal subjects.

An explanation is offered for the observations that following intravenous sodium lactate there is usually a rise in the blood uric acid, and

an increase in the body temperature and pulse rate. All of these are transitory, and are not considered as contraindications to the use of lactate.

We wish to acknowledge our indebtedness to Drs. S. A. Cosgrove, J. F. Norton and E. G. Waters for their interest in this work, and for permission to use patients on their services. Dr. Cosgrove also read and criticized the typescript.

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HORMONAL BIO-ASSAY IN A CASE OF OVARIAN DISGERMINOMA

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DISGERMINOMA of the ovary was first described in 1906 by Chevassu¹ who called it "seminoma" because of its resemblance to male testicular tissue. Since that time numerous cases have been reported in the literature. In recent years R. Meyer² has applied the logical term "disgerminoma" to it to suggest an origin from a mal-development within the gonad. It may therefore involve either the ovary or the testicle. Among those who have discussed the condition R. Meyer,³ Fauvet,⁴ H. O. Neumann,⁵ Geist,⁶ and Meigs⁷ may be mentioned. In the cases described the clinical as well as the pathologic features were extensively discussed.

Hormonal studies which are of extreme importance in solid ovarian tumors in general and in disgerminoma in particular have, however, been lacking. The only instances in which the tumors themselves were studied for the presence of hormones included a case by Gospe⁸ of a granulosa cell tumor in which estrogenic hormone was found, a similar case by Schuschania,⁹ and others by Meyer,¹⁰ Klawns,¹¹ and Neumann.¹² In the theca cell tumor group the only case studied was that of Geist and Spielman,¹³ who found considerable quantities of estrogenic hormone. For the arrhenoblastoma, Szathmary¹⁴ found complete absence of both estrogenic and gonadotropic hormones in the urine of one case. The appended chart (Table I) includes all studies from the point of view of hormones up to the present time. In some of the cases of disgerminoma attempts were made to study the gonadotropic hormone in the urine. The results have proved to be interesting. Bluemel¹⁵ collected the results obtained in the hormonal investigation of the urine of 15 cases occurring in the male testicle. In 11 cases a prolan A reaction was obtained. In a twelfth case, in addition to prolan A, following the removal of the involved testicle and the occurrence of metastases, prolan B was also demonstrated. Implants of the metastases in this case showed both prolan A and B. In a

19-year-old amenorrheic female, Fauvet¹⁶ obtained prolan A effects in the urine before operation and a prolan A and B reaction postoperatively. In another case menstruating normally, he¹⁶ found the urine to be negative both pre- and postoperatively. Implants of the tumor into immature rats were also negative.

The case here reported is another to be added to the literature and represents the first in which the extracts of the tumor for estrogenic and gonadotropic hormones were studied.

CASE REPORT

G. A., colored, 16 years old, nullipara, was admitted to the Gynecological Service of the Lincoln Hospital complaining of a mass in the abdomen. Her past history was essentially negative except for an attack of mumps one month before admission to the hospital. Her menstruation had always been regular and had begun at the age of twelve. There were no symptoms referable to the mass. Physical examination showed a well-developed and well-nourished female, perhaps slightly more mature physically than her age indicated. Her breasts were normal and showed no secretion. Her hair distribution was that of a normal female. On pelvic examination the external genitalia and vagina were found to be normal. The cervix was conical, closed, pointed posteriorly and was slightly eroded. A firm, nontender mass, smooth in contour, and moderately movable, was found in the right fornix. It extended above the pelvis to the left of the midline and about 1 inch above the umbilicus. To the left of this mass a similar structure believed to be the uterus could be felt. The left fornix could not be palpated and adnexa as such were indistinguishable.

Laboratory examinations, including Wassermann, were essentially negative. X-ray examination of the lungs and sella turcica was negative. Uterosalingography, by means of iodized oil, was attempted but the results were inconclusive. At laparotomy the right ovary was found to be completely replaced by a large, solid tumor. The left ovary was normal in size but contained a small nodule upon its surface in the region of one of the poles. The other abdominal viscera and the peritoneum were normal. Both ovaries were removed.

Convalescence was complicated by lobar pneumonia and a transitory pyelonephritis. The patient was discharged twenty-three days after operation and was referred for x-ray therapy. She was seen four months after leaving the hospital and examination of the pelvis was found to be essentially negative. She felt well and had no complaints. A Friedman pregnancy test on the urine at this time was negative.

PATHOLOGIC REPORT

Gross.—Specimen consisted of both ovaries which had been removed in toto. The right ovary was the site of a kidney-shaped tumor measuring 20 by 12 by 7 cm. and weighing 1,343 gm. It was encapsulated and its external surface was smooth and irregularly nodular. Its color was homogeneously yellowish gray, with several mottled hemorrhagic areas. On section, its consistency was found to be rubbery throughout, and its appearance lobulated. A whitish, oily fluid could be scraped from its cut surface. Normal ovarian tissue was nowhere to be found.

The left ovary measured 4 by 2.5 by 1 cm. and was essentially negative except for a small area measuring about 1 cm. in diameter, situated on its surface near one of its poles. On section this area closely resembled the tissue present in the right ovary. The nodule was circumscribed and projected above the surface of the ovary to some degree.

Microscopic examination of the right ovary showed large collections of cells which stood out clearly and stained well (Fig. 1). The cells were surrounded by connective tissue septa dividing them into lobules which varied in size, some being large and others small. Projecting from the larger fibrous septa were smaller fibrous bundles which dipped down into the lobules dividing them into smaller and smaller units, so that the final subdivisions consisted of collections of only 6 to 10 cells. The fibrous tissue was relatively dense, and scattered irregularly throughout its meshes many lymphocytes

were to be seen. In all portions of the tumor, the connective tissue dipped down and formed the supporting tissue for the cells.

The cells forming the tumor were large and their nuclei varied in size. In some the nuclei occupied almost the entire cell, so that only a rim of cytoplasm was distinguishable. In others, the nuclei were smaller, in the main centrally situated, and occasionally did not stain well. In the nuclei, at least one nucleolus could be made out. The larger nuclei stained heavily and appeared granular. The cytoplasm of the cell took a much lighter stain which was homogeneous and somewhat reticulated.

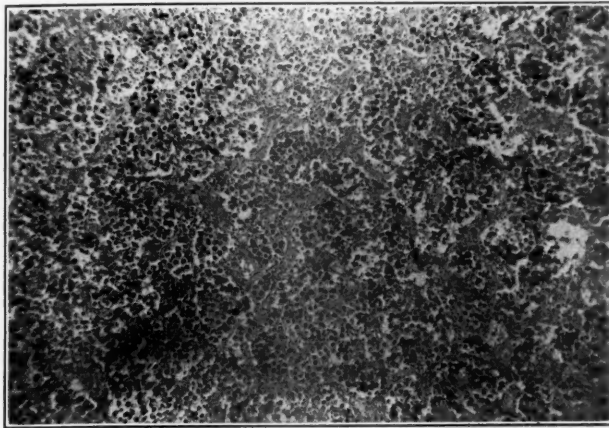


Fig. 1.—Right ovary, low power, showing the large clear cells divided into lobules as well as the large amount of connective tissue containing lymphocytes.



Fig. 2.—Left ovary. Low power. The tumor nodule situated at one pole stands out clearly. Normal ovarian tissue is sharply demarcated. The rich blood supply around the tumor is evident.

As has been mentioned, the small round cells were irregularly scattered throughout the connective tissue. An occasional large round cell, eosinophile and plasma cell, was also seen. There were no multinucleated giant cells visible. In some sections there had been considerable degeneration of the cells as well as pyknosis of the nuclei and in others the connective tissue were hyalinized. Normal ovarian tissue was nowhere to be found in this ovary.

Microscopic examination of the left ovary (Fig. 2) showed only one small nodular area which was the site of the tumor. This area was well demarcated from the rest of the ovarian stroma by connective tissue, which contained numerous blood vessels and

was situated near the surface of one of the poles. The nodular area here showed essentially the same characteristics as those of the right ovary, except that the cells rather than the connective tissue predominated. The cells of the nodule were not nearly as clearly stained, and most of the cytoplasm did not appear at all. Instead, large vacuoles were seen. The nuclei did not stain as clearly as those of the cells of the other ovary. The fibrous tissue contained small round cells but their number was not as great as those of the other side. The rest of the ovary showed the typical structure of ovarian tissue. However, ova were not present, nor could follicles either in the process of maturation or atresia be recognized. Several corpora albicantia and normal corpora lutea were present. Fat stains showed only a small quantity of fat distributed both within and outside of the cells.

HORMONE STUDIES

Extracts of the tumor tissue were studied for hormonal content. For the gonadotropic hormone the acetone method described by Frank and Salmon¹⁷ for extraction of blood was utilized. For the estrogenic

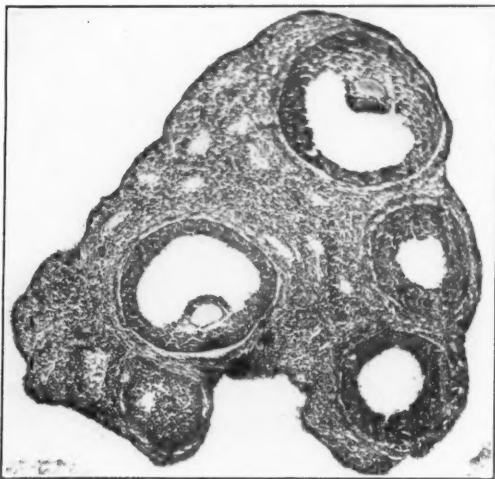


Fig. 3.—Immature rat's ovary showing follicular ripening (A.P.R. I.).

hormone the extracts were prepared by using lipid solvents consisting of alcohol and ether. Gonadotropic hormonal extracts injected into immature rats showed a prolan A affect (A. P. R. 1) with the equivalent of 24 gm. of tissue (Fig. 3). A total of 60 R.U. of prolan A was therefore present in the entire tumor. Extracts for estrogenic hormone injected into castrated mice showed consistently negative vaginal spreads indicating a complete absence of the estrogenic hormone.

DISCUSSION

Table I shows hormonal studies performed upon either the urine of patients harboring solid ovarian neoplasms or the tumors themselves. As can be seen, relatively little work has been reported up to the present time. For the granulosa cell tumors there is considerable evidence that the estrogenic hormone is present in the tumor itself as can be seen by the positive results obtained from extracts of the tumor,

TABLE I. HORMONE STUDIES OF SOLID OVARIAN TUMORS*

| TUMOR | AUTHOR | BLOOD STUDIES | | URINE STUDIES | | TUMOR STUDIES | |
|----------------------|----------------------------|---------------|----------|------------------------|-----------------------------------|---|----------------|
| | | E.S. | A.P.R. | E.S. | A.P.R. | E.S. | A.P.R. |
| Granulosa cell tumor | Meyer, 1931 | | A.P.R. 0 | Pos. (pre-op.) | A.P.R. I | Pos. (im) Neg. (ex) | (im) Neg. Neg. |
| | Schuschania, 1930 | | | Neg. (post-op.) | 111 (9 days post-op.) Neg (later) | | |
| | Pahl, 1931 | | | | | | |
| | Klaften, 1932 | | | Pos. (7 days post-op.) | A.P.R. I | (ex) Pos. (im) Neg. (ex) Pos. (im) Pos. (ex) Pos. | |
| | Kaufman, 1932 | | | | | | |
| Arrhenoblastoma | Frank, 1932 | | | | | | |
| | Neumann, 1933 | Pos. | A.P.R. I | | | | |
| | Dworzak and Podleska, 1933 | | | Pos. (pre-op.) | I (pre-op.) | (ex) Pos. (im) Pos. (im) Neg. | |
| | Kleine, 1934 | | | Neg. (post-op.) | Neg. (later) | | |
| | Gospe, 1936 | | | | | | |
| Disgerminoma | Wagner, 1930 | | | | | | |
| | v. Szathmary, 1934 | | | Neg. (pre-op.) | | | |
| | Wallis, 1933 | | | Pos. (1 day post-op.) | Neg. A.P.R. I to III | | †I to III |
| | Kleine, 1934 | | | | A.P.R. I (pre-op.) | | |
| | †Blumel, 1934 | | | | A.P.R. I & III (4d post-op.) | | |
| Theca cell tumor | Fauvet, 1936 | | | | Neg. (pre- and post-op.) | (im) Neg. (ex) Neg. (ex) Pos. | A.P.R. I |
| | Authors, 1937 | | | | | | |
| | Geist and Spielman, 1935 | | | | | | |

*E.S., Estrogenic substance. A.P.R., Anterior pituitary reaction. (im), Implant. (ex), Extract. †, Performed on males. ‡, Performed on metastatic tumors. Pos., Positive reaction. Neg., Negative reaction.

from implants, and from urinary titration. The theca cell tumor in which considerable estrogenic hormone was found by Geist and Spielman¹³ suggests a definite relationship to the granulosa cell group.

The findings in disgerminoma of the ovary appear to point to an increase in prolan A. Bluemel's¹⁵ and Fauvet's¹⁶ reports showing A. P. R. I to III reactions in the urine of a male on the one hand, and a female on the other, suggest hormonal activity on the part of the tumor. This is further emphasized by the presence of prolan A in the authors' case. The significance of the isolation of this hormone in cases of disgerminoma is not clear. When associated with cases of amenorrhea in which developmental anomalies may play a part, an increase of the prepituitary hormone either in blood, urine, or the tissues themselves may be expected since an increase in the quantity of this hormone has repeatedly been observed in amenorrheic females.

Its presence, however, in males (Bluemel¹⁵) as has been stated, implies hormonal activity on the part of the tumor. No satisfactory conclusions, however, can be drawn at the present time because of the paucity of material reported heretofore, especially since there are no reports of the gonadotropic hormone content of normal tissues. It is to be emphasized that hormone studies in cases of solid ovarian tumors offer the greatest hope for clarification of the entire subject of neoplasms of the ovary.

SUMMARY AND CONCLUSIONS

1. A case of disgerminoma of both ovaries in an otherwise normal 16-year-old colored girl is presented.
2. Hormonal studies upon extracts of the tumor, the first to be reported in this type, showed complete absence of estrogenic hormone and the presence of the prepituitary hormone (prolan A).
3. Since embryologically the tumor may be traced to certain undifferentiated neuter cells in the primitive ovary the absence of estrogenic hormone is to be expected. The presence of the prepituitary hormone, however, cannot be accounted for.
4. It is emphasized that hormonal studies in cases of ovarian neoplasms offer the greatest hope for clarification of the subject.

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AN X-RAY STUDY OF GASTRIC FUNCTION DURING LABOR*

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THIS study was undertaken because it has long been our opinion that gastric digestion is often arrested during labor. The frequency of vomiting, particularly during or after anesthesia, of food which from the patients' statements, we know had been eaten many hours earlier, inevitably leads to such an impression. This observation is common among anesthetists with wide delivery room experience.

Could it be shown that there is, in general, delayed emptying of the stomach during labor, it would open for serious consideration two problems; first, a revision of the common methods of maintaining patients' nutrition and water-balance during labor, and, second, the adoption of steps to prevent vomiting during anesthesia when it is suspected that recently ingested material remains in the stomach.

Emesis during or directly after anesthesia is a definite cause of the serious post-partum complications, pulmonary atelectasis and aspiration pneumonia. These complications are not common, but none the less important. In a review of morbid cases for the past eleven years among 20,351 deliveries at the Methodist Episcopal Hospital, we found but 7 that were unquestionably aspiration accidents. The true incidence is probably higher. There has been no indexing of aspiration accidents as such. There were no fatalities. We know of two cases elsewhere in which the aspiration of vomitus during delivery caused sudden death.

In any case, vomiting is dangerous, interferes with anesthesia, and occurs all too frequently in obstetric as compared to surgical anesthesia. It is not unlikely that the same causative factors contribute to another occasional intra- or post-partum complication, namely, acute dilatation of the stomach.

We have been able to find no factual observations on gastric function during labor in the obstetric literature for the past twenty years. The authors of several textbooks points out that vomiting may occur during labor and be a disagreeable feature of anesthesia, but gastric retention has apparently not been considered hazardous. In general, they recommend that solid food be omitted but fluids given more or less freely until late in labor. In only one instance is a proscription of even fluid by mouth in the latter first stage advised.

*Presented at a meeting of the Section on Obstetrics and Gynecology, New York Academy of Medicine, May 25, 1937.

We, therefore, felt that some useful information might be gained from serial x-ray studies after barium meals during labor. Schaefer and Guthmann and Stähler have made roentgen studies on a number of women in various stages of pregnancy and the puerperium, but on none during labor. At term they found distortion and displacement of the stomach always present. Gastric activity was almost always altered, but inconstantly so. In part of their cases the stomach was flaccid with sluggish peristalsis, in the others peristalsis was increased. In either circumstance evacuation was rapid or normal, never taking more than three hours. The duodenal bulb could not be visualized.

METHOD

Our procedure has been to give six ounces of a thin barium mixture, and, after an immediate exposure, sometimes with fluoroscopy, to take three or four pictures at hourly intervals. The x-ray examinations were made with the patient standing, but she was kept in bed during the rest of the test period. No food, fluid, or medication was allowed. The length of the observation period and the necessity of the patient's cooperation made it obligatory to select primigravidas in whom delivery seemed not too imminent. None of the patients had previous histories suggestive of gastrointestinal disorders with the exception of some limited vomiting of early pregnancy in several instances. They were in active first stage labor of varying intensity. The earliest delivery occurred after barium was five hours, the latest thirty-eight hours. The results from the ten cases on whom we were able to obtain significant data are summarized in Table I.

TABLE I

| CASE | HOSP. NO. | AGE | AT BEGINNING OF TEST | | EVACUATION TIME AND COMMENT | TIME OF DELIVERY AFTER BaSO ₄ |
|------|-------------|-----|----------------------|-----------------|---|--|
| | | | DILATATION | PAINS | | |
| 1 | E. H. 18636 | 34 | 2-3 F.B. | Mod. 5-8 min. | Empty in 2 hr. | 26½ hr. |
| 2 | A. R. 19058 | 22 | 1 F.B. | Irreg. 4-8 min. | Empty in 3 hr. Sl. residue delineating mucosa. | 24 hr. |
| 3 | A. S. 18641 | 26 | 2 F.B. | Irreg. 4-8 min. | Empty in 2 hr. | 16 hr. |
| 4 | V. B. 18652 | 22 | 2½ F.B. | Mod. 4 min. | Empty between 3-4 hr. Sl. residue along lesser curvature. | 9 hr. |
| 5 | M. C. 18864 | 25 | 1 F.B. | Mod. 5 min. | Empty in 2 hr. | 17 hr. |
| 6 | H. M. 18870 | 22 | 3-4 F.B. | Mod. 3-4 min. | Empty between 2-3 hr. | 5½ hr. |
| 7 | M. G. 18930 | 26 | 2½-3 F.B. | Short 5 min. | Empty in 2 hr. | 38 hr. |
| 8 | I. M. 18977 | 26 | 2 F.B. | Mod. 5 min. | Empty between 3-4 hr. with sl. residue | 16½ hr. |
| 9 | A. W. 18912 | 26 | 3 F.B. | Mod. 3-5 min. | About 50 per cent residue at 4 hr. Apparent increase between 2-3 hr. ? Ingestion of fluid. | 6½ hr. |
| 10 | O. N. 18831 | 34 | 3-4 F.B. | Mod. 4-5 min. | At 1 hr. major portion of meal still in situ. No further pictures. After delivery vomited approximately all of test meal. | 5 hr. |

DISCUSSION

It is seen that of the completed cases but one, Case 9, shows any appreciable delay in gastric evacuation. There is some suspicion in this case that the patient may have, in addition, taken some fluid, for there was apparently an increase in the stomach contents between the last two exposures. Case 10 is included for interest, though the x-ray findings are incomplete. One hour after administration the shadow of the barium meal had not appreciably diminished. This was true in no other instance. It was impossible to take further pictures, but following delivery, five hours after the barium, she vomited what seemed to be the entire test meal.

From this small series we can say only that there is no constant or characteristic alteration of gastric evacuation in primigravidas during labor. Delay apparently occurs in some patients as an individual disturbance. There was no evidence of obstructive interference in the cases with retarded emptying. The changes are probably functional and neuromuscular rather than mechanical. Whether there may be any correlation between the severity of labor pains and the incidence of gastric dysfunction is not indicated by our data. What effect the various drugs used for amnesia and analgesia may have on gastric activity merits study.

Despite the evidence that not all patients have gastric retention during labor, we believe that the occasional arrest of digestion as demonstrated above and observed clinically warrants considerably caution in administering even fluids by mouth to any patient in active labor, although it may therefore be necessary to increase the use of parenteral solutions. When a patient has a short labor and comes to delivery after a recent meal, or when it is suspected that the stomach has not been emptied of food or fluids taken some time before, it would doubtless be wise to evacuate her stomach by lavage before giving anesthesia. We are not yet sanguine enough to suggest this as a routine for the busy delivery room; it is only the hindsight from the occasional aspiration catastrophe that strongly recommends it.

SUMMARY

1. Of 10 primigravidas studied by G-I series during labor, two showed delayed, the rest normal, gastric evacuation.
2. Since it seems that some individuals may, unpredictably, have gastric retention in labor, it is recommended that the oral route for the upkeep of nutrition and fluids be recognized as sometimes inefficient and potentially hazardous, and that precautions be exercised to avert vomiting during anesthesia.

The expenses of this study were borne by the Edwin F. Lindridge Fund.

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GRANULOSA CELL TUMORS OF THE OVARY WITH PRECOCIOUS PUBERTY

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IN THE 45 cases of malignancy of the ovary proved by microscopic examination at the Wisconsin General Hospital during the past eight years, five have been granulosa cell tumors. The age incidence in these cases has varied from five to sixty-four years. No case of bilateral involvement of the ovaries has been encountered. Every case, except that of a five-year-old girl, was treated by surgical removal of the tumor followed by x-ray therapy. There has been no known recurrence of the tumor in any of the cases. A summary of the 5 cases is given in Table I.

The particular purpose of this paper is to outline the influence of granulosa cell tumors on preadolescent girls and to report a case occurring in a five-year-old patient.

CASE REPORT

History.—D. M., aged 5 years, 2 months, was admitted to the Wisconsin General Hospital on Jan. 13, 1936. She was born two weeks prematurely by forceps delivery of a 27-year-old mother, who at the time of the child's birth had had high blood pressure and albuminuria for one month. Birth weight was 5 pounds, 4 ounces. She developed normally until June, 1935, at which time her breasts began to enlarge and pubic hair began to appear. In September, 1935, following a day of mild abdominal pain, she began to have a slight bloody vaginal discharge. Except for four or five intervals of ten to nineteen days of amenorrhea following each injection of "follutein" given by her family physician, her menstrual flow remained constant. Her breasts continued to enlarge. Her facial expression became more mature. During the six months prior to her admission to the hospital, she gained about eight pounds in weight.

Physical Examination.—Patient was a well-developed, well-proportioned child about the size of an 8 year old. Height 46 inches. Weight was 51 pounds. Optic fundi were normal. Blood pressure was 116/74. Breasts and nipples were well developed. There was an abundant growth of pubic hair. There was no axillary hair. Her hips were wide. The abdomen was slightly protuberant. An ovoid tumor about 8 by 5 cm. was palpable in the right lower quadrant of the abdomen.

Laboratory Findings.—Urinalysis, blood counts, blood sugar, and nonprotein nitrogen were normal. X-ray plate of the cranial bones was normal. Bone age, as determined by the carpal bones, was that of a child of at least 10 years. Aschheim-Zondek test was negative. No blood or urine studies for estrin were performed. Intelligence quotient was 125.

Impression.—Granulosa cell tumor of the right ovary.

Treatment.—Right salpingo-oophorectomy was performed on Jan. 31, 1936. The left ovary was normal. The uterus was slightly larger and softer than normal.

Pathology.—Right ovarian tumor measured 8 by 5 by 4 cm. It had a grayish, granular, somewhat solid, fibrous cut surface with a thick capsule. Microscopically this was a cellular tumor with granulosa cells diffusely scattered throughout the fibrous stroma. There was a tendency to form cords and nests of cells. Small and moderate sized cysts were seen to be lined by several layers of cells.

Postoperative Progress.—Beginning on the second postoperative day, a profuse menstrual flow lasted for forty-eight hours. After the eighth postoperative day there was no discharge from the vagina. By the twenty-fourth day the breasts

TABLE I. SUMMARY OF FIVE CASES OF GRANULOSA CELL TUMOR OF THE OVARY FROM THE WISCONSIN GENERAL HOSPITAL

| PATIENT | AGE | SYMPTOMS | GROSS PATHOLOGY | HISTOLOGY | TREATMENT | PROGRESS |
|---------|-----|---|--|--|---|---|
| D. M. | 5 | Continuous bleeding for 5 months | Right ovarian tumor 8 by 5 by 4 cm. Thick capsule | Mixed type | Right salpingo-oophorectomy | Regression of puberty precox. Well after 15 months |
| L. W. | 35 | Irregular menses for 6 years. Menorrhagia. Four months' continuous bleeding | Left ovarian tumor 16 by 12 by 7 cm. Well encapsulated | Solid masses granulosa cells. Hyperplasia of endometrium | Curettag, left oophorectomy, uterine suspension, x-ray therapy | Well after three years |
| T. L. | 43 | Amenorrhea 1 year. Menorrhagia for 1 year. Continuous flow for 5 years | Right ovarian tumor 22 by 17 by 12 cm. Well encapsulated | Solid masses of granulosa cells. Endometrial hyperplasia | Curettag, right salpingo-oophorectomy, supravaginal hysterectomy, x-ray therapy | Well after one year |
| A. C. | 52 | Brownish discharge 1 year. Continuous bleeding 3 weeks | Left ovarian tumor 6 by 5 by 5 cm. | Solid cellular tumor. Endometrial hyperplasia | Curettag, colporrhaphy, left oophorectomy. Fixation of uterus. X-ray therapy | Well after three years |
| E. F. | 64 | Menopause at 45. Regular menses resumed at 64 for 6 months. Continuous flow for 1 month | Large thin walled left ovarian tumor filling the abdomen | Uniform masses of granulosa cells. Low grade malignancy | Transfusion, excision of ruptured left ovarian tumor, x-ray therapy | Discharged in good health 20 days after operation. No follow-up examination |

were definitely smaller in size. A second Binet test on the twenty-fifth postoperative day showed her intelligence quotient to be 125. Re-examination on June 11, 1936, showed that there had been a definite regression of secondary sex characteristics. The pubic hair had practically disappeared and the breasts were much smaller in size. The patient was seen again on May 4, 1937. She had had no vaginal discharge. Her breasts were normal. The nipples were not prominent. No pubic hair was present. Her body configuration was that of the childhood type. The abdominal

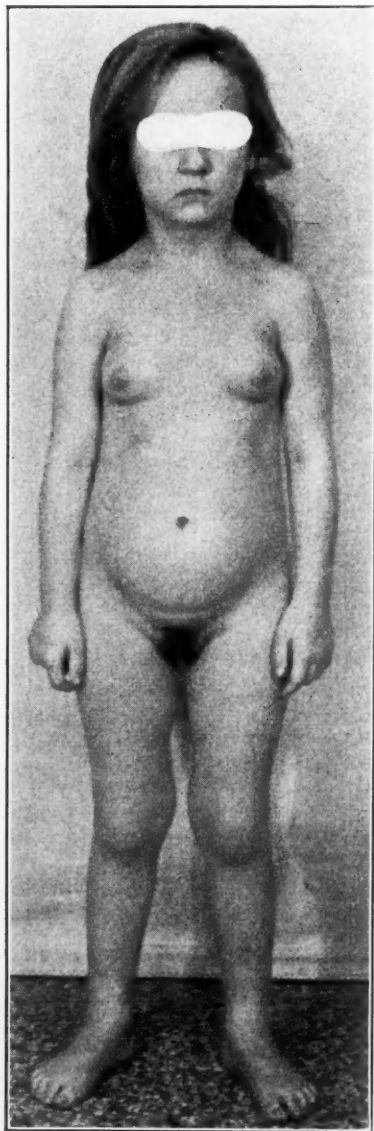


Fig. 1.

Fig. 1.—Precocious secondary sex characteristics in a 5-year-old girl with a granulosa cell tumor of the right ovary.



Fig. 2.

Fig. 2.—Precocious breast development resulting from a granulosa cell tumor in a 5-year-old patient.

wound was well healed. The uterus on bimanual examination was found to be small, forward, and movable. The fornices were clear.

DISCUSSION

A summary of the literature up to February, 1936 revealed only eight reported cases of granulosa cell tumors of the ovary causing symptoms in children under

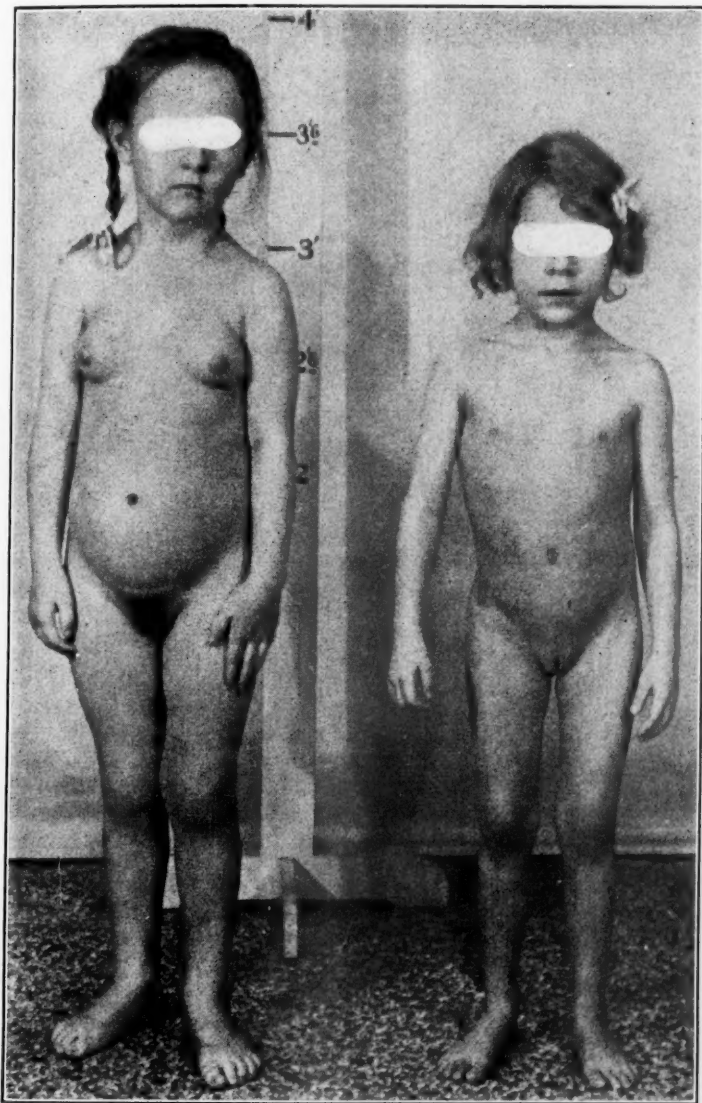


Fig. 3.—Skeletal growth compared with that of a normal 5-year-old patient.

ten years of age. Kleine has reported the youngest case with symptoms beginning at three years and five months. Practically all cases have shown the same symptoms and physical signs exhibited by the patient described above. The usual symptoms are: menstrual bleeding, marked acceleration of skeletal growth, hypertrophy of the breasts, and the development of pubic and axillary hair. Mental age is not

influenced by puberty precox. Arnold Gesell, after thorough mental studies of cases of precocious pubescence, concluded that sexual precocity had no marked effect on mental maturation. Mentality of two of the eight reported cases of granulosa cell tumors in children was definitely low. The usual abdominal finding is an unilateral tumor of the ovary. Each of eight reported cases had a palpable tumor. Aschheim-Zondek test may be positive. The excess of estrin produced by these

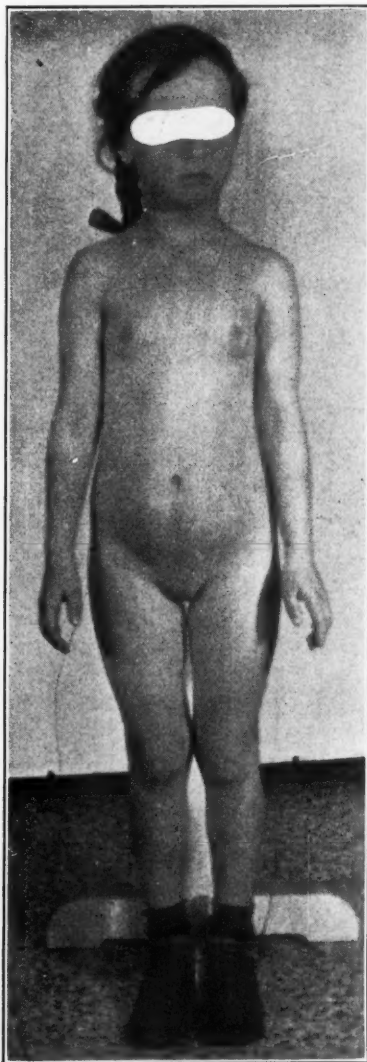


Fig. 4.—Recession of secondary sex characteristics fifteen months after removal of a granulosa cell tumor of the right ovary.

tumors is considered by Novak to be one of the strongest evidences of the direct rôle played by the female sex hormone in the normal production of sex characters.

Differential diagnosis is usually not difficult. Teratoma of the pineal body is a very rare cause of female sex precocity. Suprarenal adenomas and hypernephromas cause, in children, remarkable somatic growth and precocious development of the sex organs, but rarely cause premature menstruation. In basophilic adenomas of



Fig. 5.—Granulosa cell tumor, low power $\times 100$.

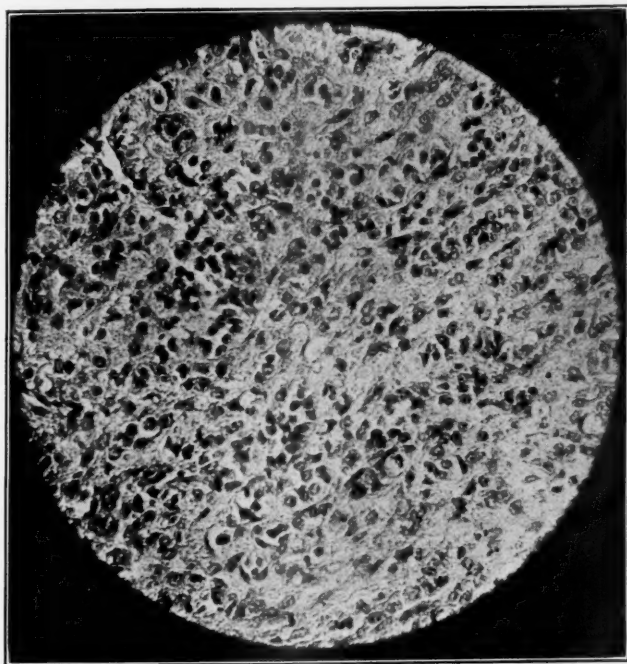


Fig. 6.—Granulosa cell tumor. High power $\times 300$.

the pituitary, the patients are usually quite fat, changes in the eye grounds are frequent, and hirsutism is usually not a marked feature.

Complete surgical removal of a granulosa tumor from a child brings about a rather rapid regression of all precocious sexual characteristics.

GALLINGER MUNICIPAL HOSPITAL

GRANULOSA CELL TUMOR OF THE OVARY*

REPORT OF A CASE FOLLOWED BY PREGNANCY

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TUMORS having a functional role, or an endocrine influence, offer an ever more interesting field; not particularly because of their rarity, but because of the possible insight which may be gained in regard to abnormal functions of the endocrine glands.

Credit for our present interest in these tumors must be given to Robert Meyer,¹ who enlightened us on the subject especially in 1930. An adenoma of the Graafian follicle, with transition to malignancy, was first observed in 1895 by von Kahliden.² Others described tumors with follicle-like areas, but no proof was given of their granulosa qualities except by von Werdt³ in 1914. Meyer, about the same time, definitely classified these neoplasms which had the characteristics of follicular epithelium into the granulosa cell group.

As to origin, the consensus of opinion leads one to accept the view of Fischel that ovarian mesenchyme is the forerunner of normal granulosa cells. Not until this genesis is established can we hope for definite proof of the origin of granulosa cell tumors, but at present, both are considered to arise from the mesenchyme of the ovarian anlage.

Of the ovarian tumors, the granulosa cell type has been found to comprise 0.9 per cent (Szathmary), 1.4 per cent (Fauvet), and 4.04 per cent (Klaften), or an average of 2.11 per cent in a series of 1,728. The majority of cases, out of a total of approximately 250, are unilateral. The incidence in 200 cases collected by Pratt⁴ was maximal between the ages of 45 and 54 years, though they may occur at any age.

CASE REPORT

Miss C. D., 36 years of age, was admitted to the Charity Hospital on May 8, 1937. She complained of "almost continuous menstruation." Menses began at the age of 12 and were of the twenty-eight-day type, lasting six or seven days, profuse the first two days and scanty the remainder, until she reached 26 years of age. From this time to the age of 35 years, the periods occurred every two three or four months, were scanty, and lasted only two days. Beginning in April, 1936, the patient noticed varying degrees of vaginal bleeding, requiring 8 napkins on some days and only 1 on others, except for two brief intervals. She states that she was given injections of either theelin, antuitrin-S, or progynon every two weeks from April to October, 1936, a tonsillectomy was performed and ergot was taken, all without noticeable effect. However, on stopping treatment, there was no bleeding until January, 1937. During this period of amenorrhea, she noticed that an aching pain, which had previously been present in the right lower abdomen, became "sore like an abscess" and radiated down the right thigh. The pain had since been intermit-

*Read before the New Orleans Gynecological and Obstetrical Society, April 21, 1938.

tent, worse on the days when there was only a scant flow, but never severe enough to confine her to bed. The vaginal bleeding had continued daily for the past four months with a progressive increase in pain. The patient contemplates marriage as soon as her health will permit.

Physical examination revealed a white female, weighing 140 pounds, with the normal distribution of fat. The breasts were slightly larger and more pendulous than one would expect. The distribution of hair was normal. There was a moderate secondary anemia. Vaginal examination showed a nulliparous introitus and healthy cervix. The uterus was freely movable, of normal consistency, and was enlarged to the size of a six weeks' pregnancy. The right ovary was prolapsed, enlarged, and movable.

With a preoperative diagnosis of endometrial hyperplasia and cystic right ovary, the patient was operated upon May 11, 1937. A dilatation and curettage produced a large amount of endometrial tissue, grossly hyperplastic. A midline abdominal

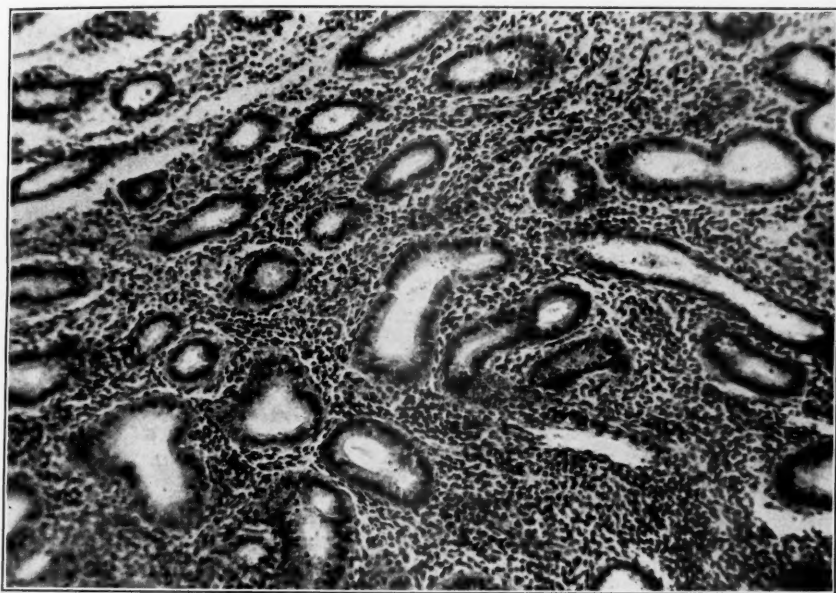


Fig. 1.—Typical hyperplasia of endometrium.

incision was made and the uterus was found to be enlarged. The right ovary was completely replaced by a tumor measuring 4 by 3 by 3 cm., and lay free to the right of the cul-de-sac. The left ovary appeared grossly normal, and there were no follicles or evidences of recent corpora lutea. Since there was no apparent peritoneal or lymphatic involvement, and the growth was grossly a well-encapsulated granulosa cell tumor, right salpingo-oophorectomy and appendectomy were performed. Cut section of the tumor showed a solid, grayish pink, granular mass divided by numerous trabeculae. It resembled somewhat a section of hob-nail liver. Microscopic examination proved this to be a folliculoma type of granulosa cell tumor. The patient was discharged on the twelfth postoperative day, after an uneventful recovery.

Several days later the patient had "soreness" in the lower abdomen and temperature ranging from 99° to 102° F., which lasted for two weeks or until the onset of menstruation on June 11. The flow was profuse for eight days, requiring bed rest, and accompanied by slight "cramps" the first two days. "Vaginal bleeding" continued as before the operation until July 1 when her physician was

consulted. She returned to the hospital and received 6 daily injections of a luteinizing hormone, which caused a cessation of bleeding after two days. On August 11, September 8, and October 8, normal menstruations occurred, lasting six days. The patient married September 21, "thinking her troubles were over." However, the next period was delayed until November 23 and was preceded for two weeks by pain in the left lower abdomen. At this time there was a dark bloody flow having a foul odor for eight days, followed by "spotting" until December 8, when a regular or normal period began and lasted five days. On December 18, she noticed nausea and pain in the left lower abdomen, both of which lasted about one month. There has been no subsequent bleeding.

An examination April 18, 1938, revealed marked enlargement of the breasts and an intrauterine pregnancy with the fundus 22 cm. above the symphysis pubis. Fetal movements were palpable.

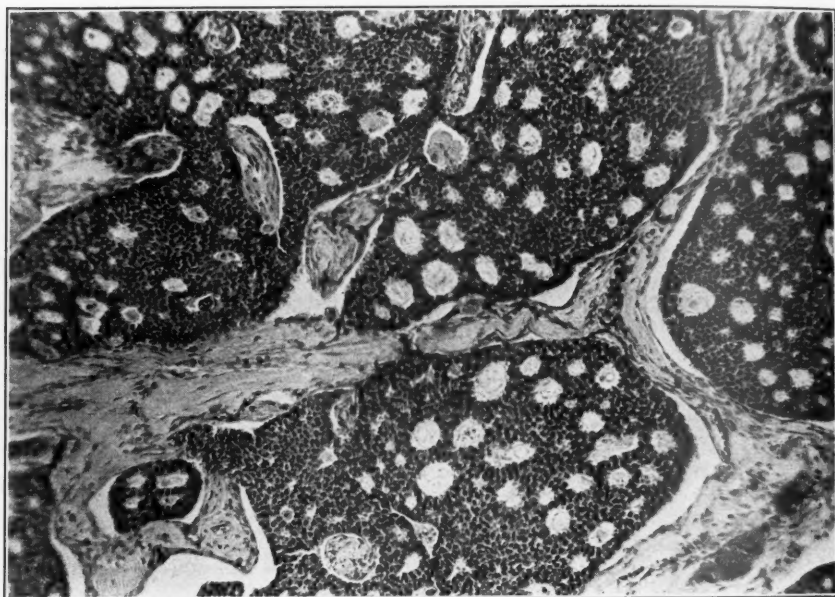


Fig. 2.—Folliculoma type of granulosa cell tumor.

Unfortunately, I have no hormone determinations in this case, but for this reason, I have given the detailed calendar history. An attempt will be made to correlate the clinical features of the case with the existing pathology.

Why should the above patient have had periods of amenorrhea for nine years, followed by a more frequent symptom, irregular and excessive menstruation?

Schulzes describes the case of a woman twenty-seven years of age with a five-year sterility, who had always menstruated profusely and regularly until the two years previous to operation, during which the menses occurred every one or two months and were scanty. Two years after a left salpingo-oophorectomy because of a granulosa cell tumor, the patient gave birth to a full-term child.

The fact that a pregnancy occurred within three months after marriage or six months after operation, proves, at least in the above described case, that there is a rapid return to normal of the hormonal and reproductive system, following removal of the granulosa tumor. There is every possibility that sterility should occur in the presence of this tumor because of the marked hyperplasia of the endometrium and lack of ovulation. The absence of follicles and corpora lutea in the ovaries substantiates this view.

CONCLUSIONS

Though it is clinical conjecture, these cases of pregnancy suggest that (1) large doses of estrin over long periods of time would have no permanent ill effects on the reproductive system. (2) By controlling endometrial hyperplasia with luteinizing hormones and assisting ovulation, pregnancy is more likely to take place.

In those cases in which an endometrial study has been made (Fig. 1), a cystic type or hyperplasia is almost invariably found. If it is possible to assume that a hyperestrinism existed for ten years, then the periods of amenorrhea can be explained, for it has been shown that there is a fall in level of estrin just prior to the onset of menstruation; an estrin secreting tumor would prevent this normal cyclic drop. In an uncomplicated endometrial hyperplasia, there are frequently periods of amenorrhea, though there may be a surprising regularity of menstruation, if indeed it can be called such. Novak⁷ refers to the bleeding associated with hyperplasia as "anovulatory menstruation," or periodic bleeding without ovulation. This is not a true menstruation, but rather hemorrhage from pin point areas of necrosis.

There are recorded in the literature two cases of pregnancy occurring after the removal of granulosa cell tumors and several others associated with sterility. Klaften's⁵ patient had never menstruated at the age of 29 years, at which time the tumor was removed. Regular menstruation began after one year and the patient gave birth to one child. Ten years elapsed and a period of three years' amenorrhea preceded a second operation, when a retroperitoneal tumor of the same granulosa type was removed.

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Vayssière: **Etiology and Medical Treatment of Pruritus Vulvae**, Gynéc. et obst. 36: 209, 1937.

For immediate relief, the author advises cold baths of short duration, with careful drying. Among the etiologic factors he mentions urinary infections, oxyuria, trichomonas, diabetes, pelvic cellulitis, fibroids, salpingitis, albuminuria and endocrine disturbances.

During pregnancy, pruritus is usually due to mycosis, trichomonas or bacterial infection. Treatment must be directed against these organisms. In cases due to an endocrine disturbance, administration of estrogenic substance is the treatment of choice.

J. P. GREENHILL.

STATUS OF THE THECOMA AND ITS RELATIONSHIP TO THE GRANULOSA CELL TUMOR

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THEcretory tumors of the ovary have in the past decade come much to the fore. The granulosa cell tumors as are now well established, present many vagaries of morphology, ranging from the immature fibromatoid to the mature folliculoid type. From this group a new entity has been segregated. In 1932 a series of cases of lipoid-containing tumors, desmoid in nature, with more or less marked degree of luteinlike transformation of the cells was reported by Löffler and Priesel as cases of "fibroma thecocellulare xanthomatodes ovarii." In 1934 these authors reported four more such cases.¹ This suggestion has been accepted in Europe by Schiller, Brosig, and others. In this country Melnick and Kanter² reported two similar cases and Geist³ reported 5 such cases. This type of tumor is now commonly referred to as "thecoma."

In marked disagreement with this new concept are many gynecologic pathologists. Strongly opposed to the segregation of these tumors are Novak and Gray,⁴ who draw attention to the fact that both the granulosa cell and the theca cell have a common origin from the embryonic ovarian mesenchyme. From the further fact that the biologic properties of these tumors seem to be similar, these authors see no reason for distinguishing this small "thecoma" group from the granulosa cell tumors. It was suggested by Novak that it might be more appropriate to designate this whole group as "progranulosa cell" tumors.

The purpose of this paper is not to try to settle this problem but to present an interesting case in which there are neoplastic elements markedly resembling both granulosa and theca cells. This case has been reviewed by Schiller, who believes it to be an unusual case of combined thecoma and granulosa cell tumor.

CASE REPORT

Mrs. I. W. (c10486), a white female, aged 59 years, mother of four children, was admitted to the Michael Reese Hospital on July 16, 1936. She complained of sudden onset of uterine bleeding which was pseudomenstrual in type, after having experienced her climacteric ten years previously. Three months before being seen by one of us (J. P. G.) she first noted vaginal bleeding which simulated in every way a menstrual period except that it lasted three weeks. Since then she had several short periods of bleeding which ceased, only to return after a free interval. The last flow of blood ended two days prior to operation. The breasts were large and pendulous. Pelvic examination revealed an enlarged, soft uterus one and one-half times the normal size and a tumor of the right ovary about 4 cm. in diameter. The preoperative diagnosis was granulosa cell tumor. A quantitative estrin determination of the urine on admission to the hospital, unfortunately was omitted. A supracervical hysterectomy and a bilateral salpingo-oophorectomy were done. The patient made an uneventful recovery.

Examination of Specimen.—Gross: The specimen consisted of the supracervical portion of the uterus with tubes and ovaries attached. The excised portion of the uterus measured 4 cm. in width across the fundus and 5 cm. in length. The myometrium was uniformly soft. The endometrium was very redundant and polypoid. The right ovary was firm, enlarged and measured roughly 4 by 4 by 3 cm. The external surface was nodular and focally hemorrhagic. Sectioned surface of this ovary revealed a lobulated, glistening, brownish yellow to gray mass which was mottled by yellowish dots. This mass occupied the greater part of the ovary and

measured 3.5 by 2.5 cm. At one border of the mass a firm grayish-white glistening nodule 1 cm. in diameter was present. The left ovary was atrophic. The tubes showed some evidence of fibrosis.

Histologic study of sections from the right ovary revealed that the neoplasm was circumscribed by a shell of compressed ovarian stroma. The main component cell of the neoplasm was polyhedral in shape and had a moderate-sized hyperchromatic nucleus. Mitotic figures were occasionally seen. The cytoplasm was faintly stained, finely granular, and frequently vacuolated. The cell membrane was poorly defined. The cellular arrangement formed a diffuse anastomosing trabecular network grouped about myriad sinusoids and large capillary spaces. In certain areas there was a gradual transition from this anastomosing trabecular network to a more compact cellular tissue (Fig. 1). Frequently this change was rather abrupt. Here interweaving bundles of fusiform cells with well-stained elongated nuclei gave the appearance of a distinctly cellular fibroma. From these areas thick fasciculi of the cellular fibromatous tissue traversed the neoplasm irregularly lobulating it. Frequently focal masses of epithelioid cells were festooned by fibrillar fibrous tissue or by broad fibromatous sheafs of plump fusiform cells. In certain of these focal areas the cells were quite

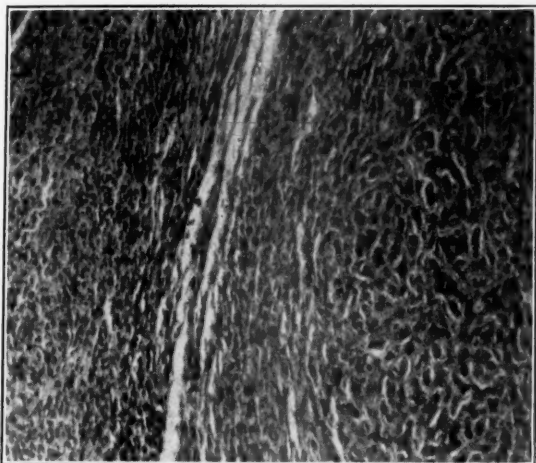


Fig. 1.—Zone of transition between a fibromatoid type of tissue (left) and an anastomosing trabecular type of epithelioid tissue (right).

large, pale staining, and epithelioid in character. The nuclei were large, oval and vesicular with well defined nucleoli. The cytoplasm was abundant and spongy. These cells had a marked semblance to lutein-like cells (Fig. 2).

The remarkable points of interest in the study of this tumor were brought out only when fat stains were undertaken. The constituent cell in the loose trabecular areas varied in its lipochromic content from scanty to moderate. In other areas the lipid content of these cells was greater; moreover the interlobular strands of fibromatous tissue in these zones were remarkably rich in sudanophilic droplets. Wherever the fibromatous tissue was in juxtaposition with masses of granulosa cells the lipid staining reaction of the former was greatly intensified. Surprising was the observation that in the solid masses of fibromatous tissue, certain parts stained heavily with sudan III, while other immediately adjoining areas of this fibromatous tissue were more or less devoid of sudanophilic lipoids. Most interesting too, was the observation that some of the focal masses of granulosa cells which gave some semblance to luteinlike cells showed but meager lipid accumulation, while the fibromatoid stroma surrounding these focal masses gave a striking reaction to sudan III (Fig. 3). Such areas call to mind the normal maturing follicle, just prior to rupture, when the granulosa cells show as yet but minimal luteinization

in contrast with the abundant lipoid accumulation taking place in the surrounding theca interna. The lipoids as demonstrated by sudan III were in the form of cytoplasmic granules or fine droplets. When studied with the polarizing microscope, there was found among the lipoids an abundance of doubly refractile crystals, i.e., cholesterol and cholesterol esters.

Microscopic study of sections of the endometrium exhibited cystic and glandular hyperplasia.

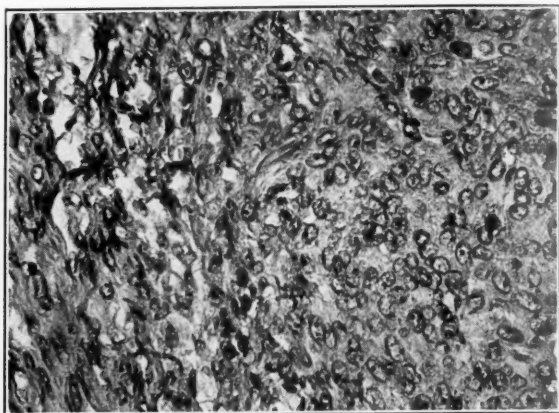


Fig. 2.—A focal mass of large pale luteinlike cells surrounded by fibrous tissue.

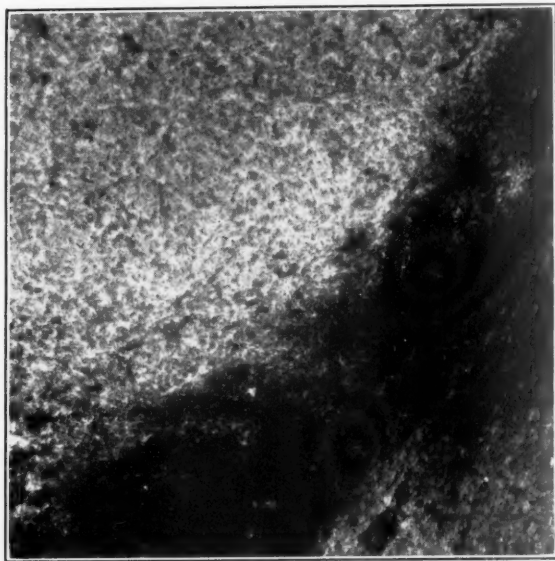


Fig. 3.—Note the striking sudanophilic reaction which photographs black in the fibromatoid tissue surrounding a focal mass of feebly luteinized epithelioid granulosa cells (upper left). The fibromatoid tissue (lower right) not in immediate juxtaposition to those cells show but scattered masses of lipoid droplets and meager luteinization.

DISCUSSION

A critical study of this case lends further support to the theory that both the theca and granulosa cells have a common origin from the ovarian mesenchyme. It is thought that the granulosa cells of the developing follicle stimulate the adjacent

undifferentiated but potential mesenchyme transforming it into theca interna. The theca interna is composed of fusiform cells which have definite connective tissue characteristics. Before maturation of the follicle, theca cells take on a distinct epithelioid appearance. After rupture of the follicle, lipid droplets accumulate in their cytoplasm. The theca cells are also active during the process of follicle atresia. Following degeneration of the ovum and of the granulosa cells, the theca cells proliferate, enlarge and accumulate lipid, a pseudoluteinization.

Both theca lutein cells and granulosa lutein cells contain lipoids. Granulosa cell tumors as a rule do not, to any marked extent, show lipid accumulation. It has long been recognized that some granulosa cell tumors undergo certain degrees of so-called luteinization. Klasten⁵ in classifying granulosa tumors included a "luteiniformis" variety. In 1910 and again in 1927 Lecène described an ovarian neoplasm rich in fat and lipoids which Moulonguet termed "folliculome lipidique."⁶ Plate⁷ in 1933 reported a third such case. A study of Plate's illustrations, which are in a measure a replica of Moulonguet's, convinces one of the granulosal nature of the tumor in spite of its richness in lipoids. In 1934 Novak and Brawner⁸ reported a large series of granulosal cell tumors. Their Case 28 resembles a spindle-cell sarcoma in which numerous bands and islands of luteinlike cells were found. Marked lipoidal changes were demonstrable by differential staining. They believed their case to be a granulosal cell tumor of the "folliculome lipidique" type.

Reports of so-called luteomas or lutein cell tumors appear in the literature from time to time. Those which are not hypernephroid ovarian neoplasms are probably nothing more than excessively luteinized granulosa cell tumors.* A rare exception indeed, however, is Pierre Masson's case of "epitheliome du corps jaune" illustrated in his book.⁹ The case reported by Wills and Romano¹⁰ in 1935 was found on further study by another gynecologic pathologist to be a hyperluteinized granulosa cell tumor.

The term luteinization should be used with caution. The endometrium very accurately mirrors the endocrinopathies of the ovary. The word luteinization when applied to granulosa cell tumors, should be reserved for those cases in which the endometrium shows premenstrual or pro gravid changes. Luteinization and excessive cellular lipid accumulation are not synonymous. By far the greater number of cases referred to in the literature as luteinized granulosa cell tumors because of their abundant lipid content, exhibited glandulocystic hyperplasia of the endometrium. This is characteristic of excessive estrogenic stimulation and not of luteinization. Perhaps the term pseudoluteinization is a better one for the cases in which the endometrium is hyperplastic, but not in the secretory phase.

CONCLUSIONS

With the evidence at hand, it is apparent that pseudoluteinization is not the distinctive feature of thecomas alone. Furthermore the purely fibromatoid character of thecomas is not a feature peculiar to such tumors, but is also seen in the immature, homogeneous type of granulosa cell tumor. It is now fairly well established that in the embryologic development of the ovary, granulosa cells are formed in loco from ovarian mesenchyme, from which likewise is formed the thecal and stromal tissue of the ovary. Since these cells have the potentiality of forming granulosa cells, which, however, have missed contact with the ovulum, they may, in developing, exhibit their inherent congenital and constitutional tendencies. In so doing, they may exhibit every step from the fibromatoid to immature trabecular formations to cordlike structures, and also to simulate follicle formation. This explains the great variation in histologic descriptions reported in the literature ranging from sarcomatous to carcinomatous changes.

Polariscopic examination of the lipoids in thecomas reveals that they are for the greater part doubly refractile, i.e., cholesterol and cholesterol esters. The lipoids in

*Since writing this paper Traut and Butterworth have published an excellent study in the *AM. J. OBST. & GYNEC.* 34: 987, 1937, in which they show that experimentally produced granulosa cell tumors in the mouse ovaries frequently resemble lutein tumors.

the case of "folliculome lipidique" studied by Moulonguet, which was without doubt a luteinizing granulosa cell tumor, were also doubly refractile. In our own case an abundance of doubly refractile lipoids was also observed.

SUMMARY

An ovarian neoplasm is reported composed of broad sheafs of xanthofibromatous tissue interlobulating masses of granulosa cells of the diffuse trabecular type. The transition between the two types of tissue frequently was not sharply defined. Sudan III stains revealed that the granulosa cells exhibited meager to moderate pseudoluteinization. The fibromatoid tissue for the greater part showed intensive cytoplasmic accumulation of fine lipid droplets. Where the fibromatoid tissue surrounded focal masses of granulosa cells, the peri-epithelial sudanophilic reaction was greatest. This process is strikingly analogous to the maturing normal follicle prior to rupture, when only feeble luteinization of the granulosa cells is present in contrast to the abundant lipid deposition of the theca interna.

It is felt that the tumor herein reported provides sufficient evidence to bridge the gap between the "fibroma thecocellulare xanthomatodes ovarii" (thecoma) and the "folliculome lipidique" of Lecène, linking those tumors which exhibit similar biologic properties into one group originating from a common type cell of the ovarian mesenchyme, the progranulosa cell.

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PRIMARY GIANT GRANULOSA CELL TUMOR OF RETRO-PERITONEAL ORIGIN WITH DEVELOPMENT INTO THE MESOSIGMOIDEUM

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TUMORS that take their origin in the organs and tissues back of the peritoneum are of infrequent occurrence. The most frequently occurring tumors are those of the kidneys, adrenal glands and the pancreas, and these originate above the umbilicus. Retroperitoneal tumors originating below the latter are rare, and a primary retroperitoneal tumor consisting of granulosa cells, therefore of ovarian tissue, and developing far away from the normal location of the ovary is even less frequently observed. For this reason the case in hands seems worth while reporting, especially as it was difficult to make the histologic diagnosis. In addition, the case may throw light on the genesis of granulosa cell tumors by reason of its inception far from the ovary and back of the peritoneum at a spot where once was the germinal cell tract (Keimbahn).

CASE REPORT

A woman, 51 years of age, presented herself two years ago, because of increasing girdle obesity which did not yield to rigid dieting. She had ceased menstruating and

thought that this might be the cause of the gain in weight. Three years previously she had had a supravaginal hysterectomy because of numerous large myomas. At the time, apart from the myomatous uterus macroscopically there appeared nothing pathologic about the ovaries or the surrounding pelvic region. On examination there was a tumescence affecting the entire abdomen and extending upward under the costal arch. It looked like a pregnancy in the ninth month. The consistency of the tumor was firm-soft, with indistinct fluctuation. Pregnancy was out of the question because of the previous hysterectomy. On the other hand, it could have been a myoma arising at the point of amputation, but the small pelvis was free of tumor except for the extension of the large mass. No connection with the cervical stump could be shown. The possibility of an ovarian tumor was excluded inasmuch as both ovaries could be recognized by touch as little atrophied bodies. By elimination, therefore, a mesenteric cyst was diagnosed, with some likelihood of a softened myoma.

An attempt was made to establish intra- or retroperitoneal origin. Hesse's symptom is supposed to be of value in such cases, namely, a difference of some degree in the skin temperature of both legs. The symptom is ascribed to the pressure on the sympathicus. It is claimed that tumorous growths too small to be palpated have been discovered through this symptom. In this case, however, Hesse's symptom was not present, either because it is a first symptom which, in this case, had disappeared with gradual adaptation to the pressure from the tumor, or because the tumor, soft as it was, had projected itself into the abdominal cavity without exerting appreciable pressure on the sympathicus. The patient demurred at an x-ray examination because of the cost, so the operation was performed under the diagnosis of a mesenteric cyst or a softened myoma.

On opening the abdominal cavity, which showed no ascites, an enormous tumor was disclosed. It filled the entire abdominal cavity and had forced the intestines upward; only after further section of the cavity could it be moved, and then it was possible to establish that the tumor lay in the mesosigmoideum. The mesosigmoideum was divided in the direction of its vessels and the tumor was carefully isolated without opening a blood vessel. As the size made it unwieldy and the tumor itself fluctuated to touch, it was punctured and 3,500 c.c. of bloody serous fluid were drawn off. The tumor was still further separated, and it became evident that it originated on the left of the spinal column about where the ureter and the large vessels cross each other. It had developed toward the front into the abdominal cavity between the two layers of the mesosigmoideum.

The monster tumor was covered with a smooth capsule of connective tissue, which was nowhere perforated. In some places it was 1.5 cm. thick and coarse, in others it was as thin as a spiderweb and tore easily. The interior was of sponge-like tissue, which radiated from the periphery toward the center and was interspersed with cavities varying from the size of a cherry to that of a hen's egg. The center was a large cavity and like the smaller cavities it was filled with a bloody serous fluid. Extensions of the tumorous tissues projected themselves into this cavity like the fingers of a polyp, and floated about there freely (Fig. 1).

The pathologic diagnosis based on a frozen section was "medullary carcinoma of the mesentery, probably metastatic." This diagnosis was not entirely convincing. First of all, there was nothing like a perforated capsule. Then, too, there was the striking presence in the section of such areas, as in Fig. 2, where in the midst of solid tumor tissue there were visible areas showing an alveolar structure. The rounded oval mass of cells in the center was surrounded by a palisade-like layer of cells. At other places there was a tendency to form "follicle-like" cavities. All this roused the suspicion that there might be here a case of granulosa cell tumor. A microscopic section was, therefore, sent to the pathologist of Loyola University Medical School. The following was the diagnosis:

"The microscopic slide reveals a tumor consisting of small epithelial cells of equal size, with distinct nuclei, all of them equally stained, of equal size and shape. The cells are arranged in strands forming tubuli, which on longitudinal as well as transverse section, consist of many layers of cells. The cells are of cuboidal shape, their nuclei somewhat spindle-shaped. The lumina of the tubuli contain fibroblasts

and wandering cells (histiocytes) and a poorly stained secretion. Other areas show masses of cells of the same type, irregularly arranged. The vessels (capillaries) contain many polymorphonucleated cells. The connective tissue is poorly developed, but follows the epithelial cells throughout the entire tumor.

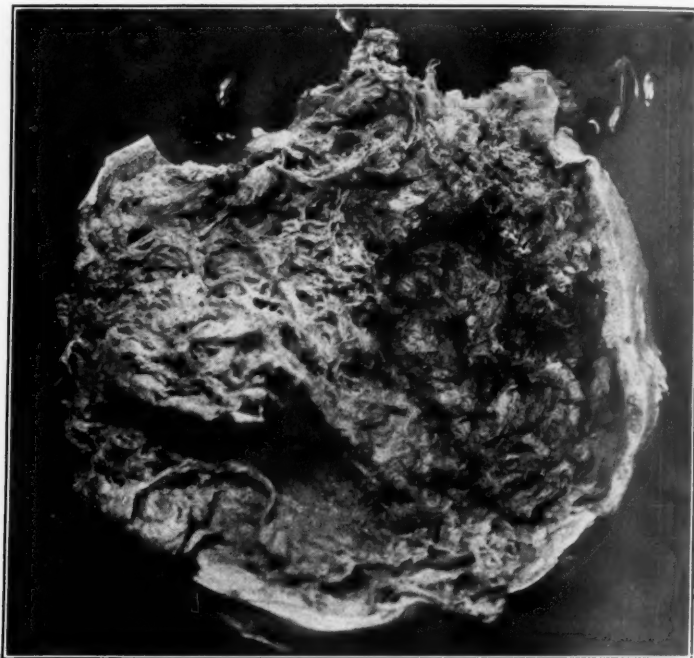


Fig. 1.—Cross section of tumor showing spongelike tissue.



Fig. 2.—Part of tumor with follicle-like arrangement. (Magn. 170 diam.)

The tumor is evidently of embryonic origin, its cells well differentiated (i.e., not of an immature type, but embryonic). The origin of the tumor is probably the ovary. The tubular arrangement of the cells resembles the arrangement of the cells of Pflüger's tubuli (Pflüger's Schläuche). There are no follicles present in the entire slide.

Tentative Diagnosis.—Embryonic ovarian tumor, not malignant, probably originating from Pflüger's tubuli or granulosa cells of the ovary.

Meantime mice were being treated with the fluid contents of the tumor. The animals injected with the unfiltered fluid all died, evidently owing to the human blood content. Treatment with the filtered fluid caused in immature mice enlargement of the uterus which is peculiar to folliculin.

A section was sent to Dr. Walter Schiller who replied: "The tumor is a typical granulosa cell tumor, ripe, no indication whatever of malignancy."

The question arises, what justifies the diagnosis of a granulosa cell tumor? As in the case of all tumors, the presumption is that the tumor preserves to a degree the form, arrangement, and functioning of the mother tissue. Small tumors afford the best prospect of being recognized as to origin and developmental progress. The huge mature tumor in this case would accordingly be a less fit object lesson. Nevertheless it affords clues enough for the diagnosis.

Among the characteristics of granulosa cell there is their follicle-like arrangement, their tendency to form roundish cavities bounded by bands of cells. The tendency to this disposition can be noticed at many places in the tumor under discussion. In addition, there is the formation of Call-Exner corpuscles, characteristic mark of follicular epithelium. These corpuscles were at first thought to be newly formed ova, but later Thomsen showed that this formation is an hydropical swelling of granulosa cells, the remains of which are at first still in evidence but later liquefy, leaving an open lumen. The process is the same as with the formation of the follicular cavity. It is a physiologic process and serves to produce the liquor folliculi. At first the cells grow around the gap that takes shape without a change in their arrangement. It appears to be a reaction peculiar to granulosa cells that they grow rosette-wise about a large cell. This reaction must evidently be traced to the relation between egg cell and granulosa. It seems to result also in individual swollen granulosa cells, and to be retained also with tumor growth.

The granulosa cell tumors have a place of their own partly showing up a readily discernible connection with the normal granulosa and partly displaying no resemblance at all with normal ovarian cells. There is no uniform theory as to the derivation of these tumors. The tumor in the case under discussion deserves special attention on account of its atypical point of origin so far away from the ovary, thus apparently bearing out Fischel's contention that the granulosa is derived from the mesenchyma. Granulosa cell tumors often present connective textural forms of growth which remind one of fibromas or sarcomas. This seems to speak for their mesenchymal origin. According to Pflüger, Waldeyer and Hertwig the granulosa cells are derivatives of the germinal epithelium (the epithelium of the plica genitalis). But thus it cannot be explained how granulosa cell tumors can originate in the ovary of women after the menopause or, as in this case, far from the ovary as a primary tumor. All the difficulties in explaining the histology of granulosa cell tumors are solved by the research work of Fischel, who proves that the granulosa cell originates in the mesenchyma through differentiation called forth by the formative stimulus of the primitive sexual cells after the latter have made their distant migration to the spot. According to Nussbaum, Galton, Boveri, and Beard the sexual cells follow a course of development which differs altogether from that of the other somatic cells, and they retain the totipotency which is essential to the first offshoots of the fertilized ovum. So the primitive sexual cells (archygonoocytes) are the mother cells of sperm cell and ovum. The latter are not the derivatives of the fertilized egg.

In Fischel's opinion there occurs no mutual intergrowth of germinal epithelial cells and the underlying embryonic connective tissue. But the connective tissue cells directly under the germinal epithelium begin to multiply more vigorously than the others. What was styled "epithelial core" before is as a fact a "mesenchymal core." Primary sex cells (archygonoocytes) are found scattered about in this mass. The formation of the plica genitalis out of the coelom epithelium and the mesenchyma never begins until the primitive sex cells have penetrated to these sections. Sometimes the granulosa cell tumors show purely connective textural forms of growth, thus presenting appearances of fibromas or sarcomas. The author is in possession of a fibromatous ovarian tumor which had caused an enlargement of the uterus, so that the patient thought she was pregnant. At the same time, how-

ever, there were mild hemorrhages of brief duration at irregular intervals on account of proliferation of the uterine mucosa and subsequent necrosis. The fluid extracted from the tumor contained folliculin as proved by the biologic test. Such tumors apparently speak for the mesenchymal origin of the granulosa cell. They seem to be a lower state of development and seem to change into epithelial forms later.

A transformation of epithelial forms of growth into growth of connective tissue is not very plausible. Embryologic research has moreover shown that epithelial formations can proceed from the mesoderm. In granulosa cell tumors there are transitional forms which belong neither to the epithelium nor to the connective tissue (Fig. 3). The tissue of the granulosa cell tumor as well as the connective tissue are thus in relation with each other by means of intermediate forms which gradually and uninterruptedly keep changing to one another.

The case described is evidently that of a granulosa cell tumor which developed at an unusual point of the germinal cell tract (Keimbahn) far away from the ovary and in the case of a climacteric woman in whom ova capable of maturing are no longer present and consequently no granulosa cells are formed. It would be interest-

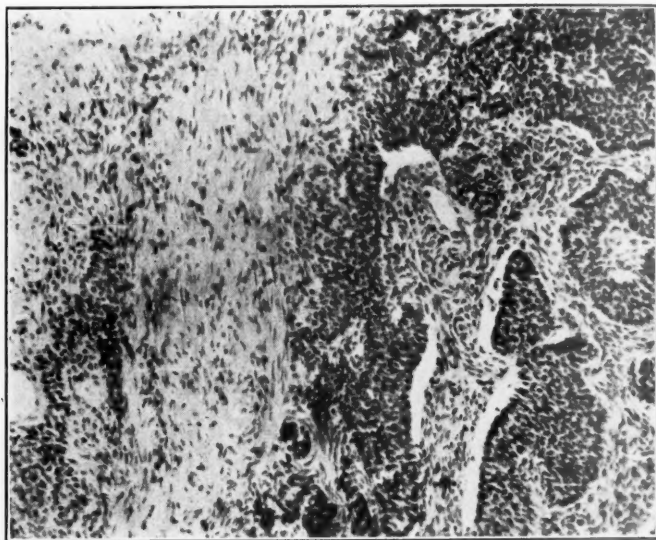


Fig. 3.—Tumor with granulosa cells, connective tissue, and transitional cell forms between the two.

ing to pursue the point as to what was the solvent stimulus which in the case of this woman caused tissues at one point of the germinal cell road to turn to granulosa and develop tumor fashion. It is known that estrin (folliculin) has an antagonistic effect upon the gonad-stimulating hormone of the anterior pituitary, and that after the ovaries ceased functioning there is an overproduction of the pituitary hormone. This could not influence the functionless ovaries but could stimulate immature cells of the germinal cell road to transform into granulosa and develop tumor fashion.

SUMMARY AND CONCLUSIONS

1. The case presented is a granulosa cell tumor as shown microscopically and biologically.
2. It developed far from the functionless ovaries as a primary tumor.
3. This seems to support the opinion of Nussbaum, Boveri, Beard and others of the independent development of germ cells and somatic cells and their migration via the "Keimbahn" to the place where the sex glands develop.

4. It seems probable that some of the germ cells (archygonocytes) remain at some place in the germ cell road and give cause to tumor formation.

5. The stimulating agent in this case was perhaps overproduction of pituitary hormone after the ovaries lost their antagonistic effect upon the anterior pituitary.

6. This case seems to support Fischel's mesenchymal theory of the granulosa cell, since the connective tissue can assume very different forms and may have developed into granulosa under the influence of arrested germinal cells and pituitary hormone.

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6633 SHERIDAN ROAD

THE TREATMENT OF LATE ABDOMINAL PREGNANCY*

WITH REPORT OF TWO CASES

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THERE is no single answer to the question, "What is the therapy of extrauterine gestation?" Treatment depends on a number of factors, such as the viability of the fetus, the time of diagnosis (whether preoperative or operative), the presence of complications, and the laparotomy findings.

As to the time of operation, Beck¹ states: "Laparotomy is indicated as soon as the diagnosis is made. If, in the interests of the child, it is desirable to postpone operation, the latter should be done about two weeks before term." According to Titus,² the thirty-sixth week is the optimal time for operation if saving the child is the primary consideration. He adds that, if fetal death is discovered, some authors prefer to defer operation for a week or so, believing that thrombosis of the placental blood vessels will lessen hemorrhage. Anspach³ advocates waiting six or eight weeks. Hellman and Simon,⁴ in their review of the literature, discredit the waiting policy because of the maceration and sepsis likely to follow fetal death and placental separation.

At operation, the chief problem is the management of the placenta. It should be handled as little as possible until the child has been delivered. There are then three courses of action: First, it *must* be removed if the site of its implantation permits. Second, if, because of its adherence to vital structures, the placenta cannot be disturbed, it may be left for absorption, and the abdomen closed without drainage.

*Read before the Section of Obstetrics and Gynecology of the New York Academy of Medicine on October 26, 1937.

The third procedure is marsupialization; that is, the thickest edges of the membranes are sutured to the margins of the incision, and the cavity is packed and drained. The placenta separates bit by bit. This method is imperative if infection is present or imminent; it has the added advantage of facilitating the control of hemorrhage by packing if placental separation occurs.

Eisaman and Ziegler's⁵ patient had a bilobate placenta. The upper lobe, connected by a narrow isthmus of tissue to the lower lobe only, was removed. The lower lobe was the larger, and the cord was attached to it; it was adherent to "the posterior surface of the uterus and broad ligament and to the right wall of the pelvis." It was left in situ and the abdomen closed without drainage. After two weeks, sepsis set in; drainage from the wound lasted for several days. Both mother

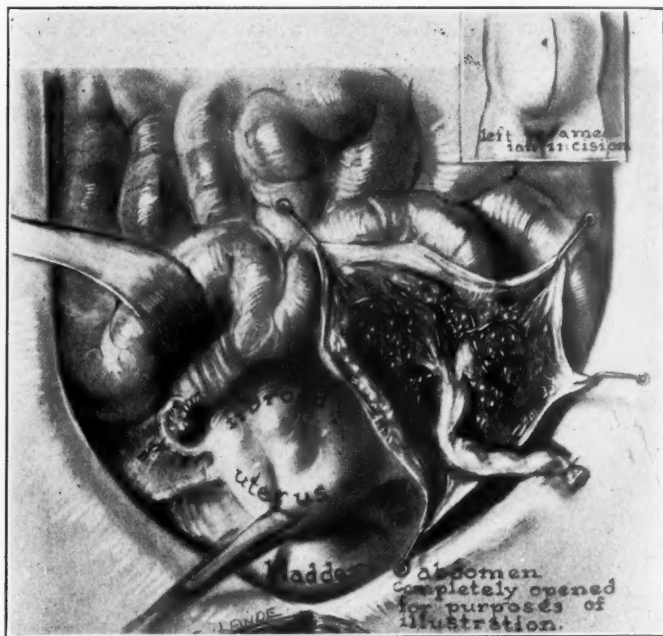


Fig. 1.—Case 1. Left paramedian incision. Abdomen opened in drawing for purposes of illustration so that fibroids and position of placenta and membranes can be seen. Intestines are distended.

and child survived. Best⁶ employed marsupialization in an emergency operation following abdominal hemorrhage at about four months. The mother was discharged in forty-nine days, after a stormy convalescence. Autopsy in a previous case of the present author's⁷ showed the placenta so firmly adherent to the intestines, left ovary, mesentery, and left broad ligament that removal would have been impossible.

REPORT OF CASES

CASE 1.—J. B. (Harlem Hospital No. 59832), a 23-year-old colored housewife, para ii, gravida iii, was admitted to the Harlem Hospital Sept. 5, 1935, at noon. Family and personal histories were of no interest, except for one induced abortion at four months. The patient's last menstrual period began Oct. 17, 1934; the expected date of confinement was July 24, 1935. Pregnancy had proceeded uneventfully. No life had been felt for the past two months. Three weeks before admission, slight vaginal bleeding was noticed. Pains began at 2:00 A.M., ten hours before admission; the

interval was thirty minutes at onset and from fifteen to thirty minutes at admission. Bleeding was more marked than previously.

On examination, the patient's physical condition appeared good. The abdomen was the size of a full-term pregnancy with a small baby. No contractions were felt. The fetal parts could not be distinguished, and the fetal heart was not heard. There was a round mass, 6 by 6 cm., of moderately soft consistency, just above and to the right of the symphysis pubis; this was apparently attached to the uterus. Vaginal examination revealed moderate bleeding, with clots. The external os admitted two fingers; the internal os, one. No membranes or presenting parts were felt. There was a mass in the posterior cul-de-sac which felt like a fibroid.

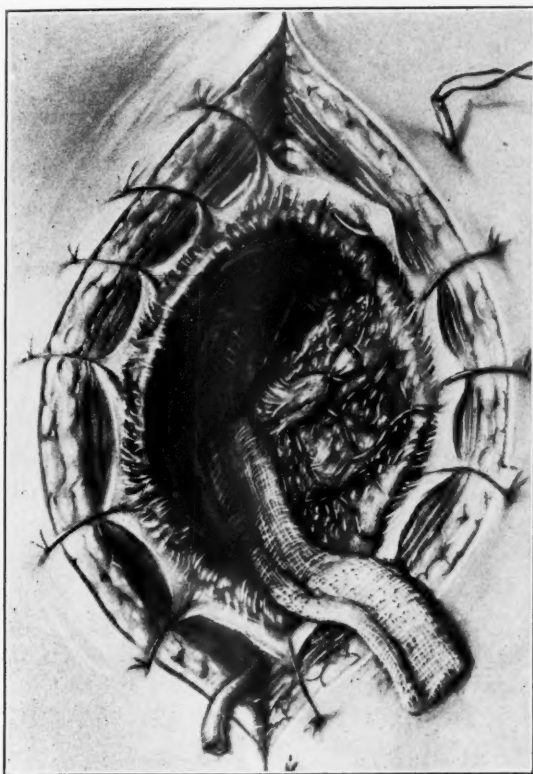


Fig. 2.—Case 1.—Illustration showing placenta marsupialized to abdominal wall. Membrane is thickened, and sutures are taken through the membranes, peritoneum, abdominal muscles, fat, and skin. Large gauze drain placed in placental tissue. In this instance less of the drain is shown than is actually used, for purposes of illustration. Incision here extends from the symphysis to the xiphoid process.

Diagnosis of abdominal pregnancy was made. This diagnosis was confirmed roentgenologically the following day; moreover, the overlapping of the sutures indicated fetal death.

Operation was performed on September 6 as soon as the diagnosis had been confirmed by roentgenogram. The abdomen was opened by a left paramedian incision. A bluish purplish sac was seen; this appeared to consist partly of membranes and partly of placenta. After the cloudy contents of the sac had been aspirated through a stab wound, the opening was enlarged and a macerated male fetus weighing 5 pounds, 4 ounces was extracted. The uterus was found enlarged to the size of a six weeks' pregnancy, with a fibroid on the posterior wall. Because of the cloudiness of the fluid, the maceration of the fetus, and the attachment of the placenta to the left

ovary, left tube, left round ligament, and mesentery of the small intestine, marsupialization was deemed advisable. The umbilical cord was ligated and cut as deeply as possible. The membranes of the sac were loosely approximated and sewn to the edges of the abdominal incision. The cavity was packed with iodoform gauze, and a Penrose drain was inserted in the lower angle. The operative wound was closed with interrupted silk sutures and dressed; a tight abdominal binder was then applied. The patient's condition was good on her return to the ward. The operative technique is illustrated in Figs. 1 to 3.

The abdominal wound drained for about three weeks after operation. The iodoform gauze was changed every two days, less packing being used each time. Because of marked anemia (hemoglobin 45 per cent, red blood corpuscles 1,520,000),

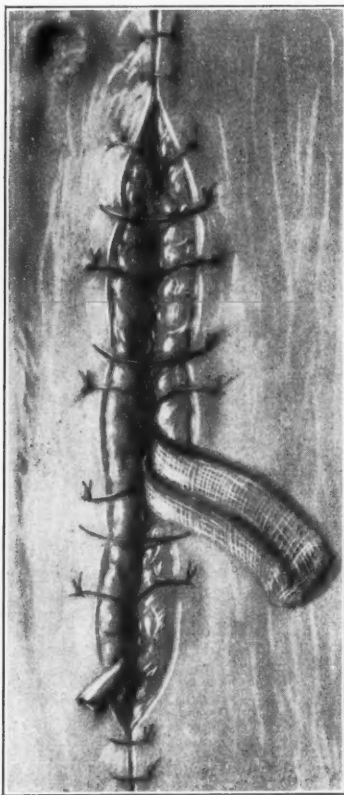


Fig. 3.—Case 1. Closure of incision. Part of gauze drain remaining outside, and at lower tip of incision a small Penrose drain is inserted into the skin, fat, and muscles.

a transfusion of 350 c.c. of citrated blood was administered on September 21, the fifteenth postoperative day. Sloughing of the placenta commenced the same day and continued for thirty-one days, until October 22. The patient was allowed out of bed on the second of November, the fifty-seventh postoperative day, and was discharged as improved on Nov. 25, 1935, the seventy-ninth day. Convalescence had proceeded uneventfully, except for anemia, and for a possible phlebitis during the first week of October. When seen again in April, 1936, the patient had no complaints.

CASE 2.—H. J. (Harlem Hospital No. 62089), a 27-year-old colored housewife, para 0, gravida i, was brought by ambulance to the Harlem Hospital at 7:15 P.M. on Nov. 26, 1935. She had had an appendectomy at the age of eleven, and a left

salpingectomy at the age of eighteen. Menstruation, which began at eleven, was irregular. The last menstrual period was April 15, 1935; and the expected date of confinement, Jan. 22, 1936. Spotting occurred in June and July. The patient felt dizzy occasionally. She began to attend another clinic on November 3. When examined at this clinic on November 24, she was told that she was perfectly well. She became ill November 26. Pains in the epigastrium, radiating to the back, occurred at intervals of from ten to fifteen minutes. The patient became very restless, vomited, and suffered from severe cold sweats.

On admission, the patient was in profound shock. She was cyanotic and restless. Blood pressure was unobtainable. The pulse was rapid and thready, the skin cold and clammy. The pupils reacted sluggishly to light. The tongue was dry, and the breath had a foul odor. The heart rate was increased. The lungs were clear. There was evidence of marked loss of blood. There was generalized abdominal tenderness, but no rigidity. A mass in the abdomen extended to three fingers above the umbilicus. The fetal outline was indefinite, and the fetal heart was not heard. On rectal examination, the cervix appeared to be dilated one finger. No presenting part was felt in the cervix. Diagnosis was either premature separation of the placenta, or ruptured uterus of unknown etiology.

Operation was performed November 26, two hours after admission. A left paramedian incision was made. A moderate amount of fluid blood escaped when the peritoneum was opened; numerous blood clots were scattered through the abdominal cavity. The fetus, lying free in the peritoneal cavity, was easily delivered, together with placenta and membranes. The membranes were attached to what was apparently the right broad ligament. There was no tube on the left side. An ovary attached to the left cornu appeared to have a corpus luteum of pregnancy. The uterus was about the size of a three months' pregnancy. The abdomen was sutured in layers without drainage. During the operation, the patient received 1,000 c.c. of normal saline and 500 c.c. of citrated blood, to which she reacted well. She was returned to the ward in fair condition. She was then placed in the shock position and given morphine sulphate, hot blankets, and another infusion of 1,000 c.c. of normal salt solution.

The fetus was that of a premature female weighing 2 pounds, 13 ounces. Autopsy showed both lungs to be purple and atelectatic, and there was moderate congestion of the cerebral vessels. The placenta measured 20 by 10 by 1.5 cm. It was composed of two lobes, to the maternal surface of one of which a Fallopian tube was attached.

The abdominal wound healed by primary intention, except for a slight superficial infection, which developed on the thirteenth postoperative day. This was followed by a pelvic cellulitis on December 10, the fourteenth postoperative day. Convalescence otherwise progressed steadily, and the patient was discharged in good condition on Jan. 3, 1936, the thirty-seventh day after operation.

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ENDOMETRIAL HYPERPLASIA (PUBERTY), ADENOCARCINOMA, FIFTEEN YEARS' FOLLOW-UP*

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THE question as to whether hyperplasia of the endometrium should be regarded as a precancerous lesion is still open for much discussion. Ewing writes: "In a series of cases of hypertrophic endometritis every gradation may be observed from normal glands to those of adenoma malignum." Taylor in 1932, after a study of adenocarcinoma cases, showed evidence that hyperplasia of the endometrium may be a predisposing factor in the later development of cancer. In this study, hyperplasia of the endometrium was found in cases of adenocarcinoma far beyond the menopause. Novak emphasized the fact that ordinary hyperplasia of the reproductive epoch is not only frankly benign from the histologic standpoint but also that it has no apparent predisposing influence in the causation of adenocarcinoma during menstrual life. Nevertheless, he found that postmenopausal hyperplasia was also associated with adenocarcinoma later in the menopause. The following case of endometrial hyperplasia with subsequent development of adenocarcinoma is reported in a girl eighteen years of age.

H. I., 18 years of age. (Hospital No. 6467.) First admission on Dec. 7, 1923. *Chief complaint:* Profuse menstruation. Mother and father died of tuberculosis. Patient had measles as a child. Had been a patient at a tuberculosis sanitarium for almost one year. *Menstrual history and present illness:* She began to menstruate at the age of fifteen years. Period was established with ease; normal, five day type. She had no dysmenorrhea and was never incapacitated. Periods were regular until 1922 when she went swimming during her menstrual period. This period lasted two weeks. It was profuse, with numerous clots. She then began to menstruate profusely every two weeks until about six weeks prior to admission when she began to flow and continued until the date of admission. During this period, she lost weight and became weaker. Examination revealed an acutely ill young female showing evidence of a marked secondary anemia and loss of weight. The lungs showed evidence of moderately advanced tuberculosis. The heart was grossly negative. Rectal: Cervix was small and posterior; uterus anterior, normal in size, shape and consistency and insensitive to motion. Adnexa and parametria were grossly negative. *Laboratory data:* Blood: R.B.C. 1,972,000; W.B.C. 8,800; polymorphonuclears 58 per cent; lymphocytes 42 per cent; Hg. 60 per cent. Urine: Negative. Blood pressure: 105/55. Sputum: Positive for acid-fast bacilli in large numbers. Operation: Dilatation and curettage, insertion of radium 50 mg. for eight hours. Gross findings: Uterus normal in size and position. Curettings considerable in amount. Microscopic: Endometrial hyperplasia (Fig. 1).

Second admission on Aug. 19, 1924. *Interval history:* After leaving the hospital patient was improved for one month. The bleeding had stopped. The following month she had profuse vaginal bleeding which lasted for two weeks. During these bleeding spells, she became dizzy and very weak. After receiving conservative treatment for several months with no success, she was advised to return to the hospital. Examination revealed a grossly negative pelvis except for vaginal bleeding. The physical findings and laboratory data were similar to those on the previous admission. Operation consisted of curettage and insertion of 25 mg. of radium which remained for sixteen hours (400 mg. hr.). The gross findings revealed the uterus to be normal in size and position, and curettings moderate in amount. Microscopic: Endometrial hyperplasia.

*Read at a meeting of the New York Obstetrical Society, January 11, 1938.

Third admission on Jan. 26, 1929. *Interval history:* Since patient left the hospital she had irregular menstrual periods but not profuse. There was no associated pain present. For about one year prior to admission, the flow again became more profuse. She was advised to return to the hospital. Examination revealed a grossly negative pelvis except for vaginal bleeding. The physical findings and laboratory data were similar to those on previous admission. She had curettage and insertion of



Fig. 1.—Hyperplastic endometritis in a girl 18 years of age after one year of profuse menstruation. ($\times 200$.)

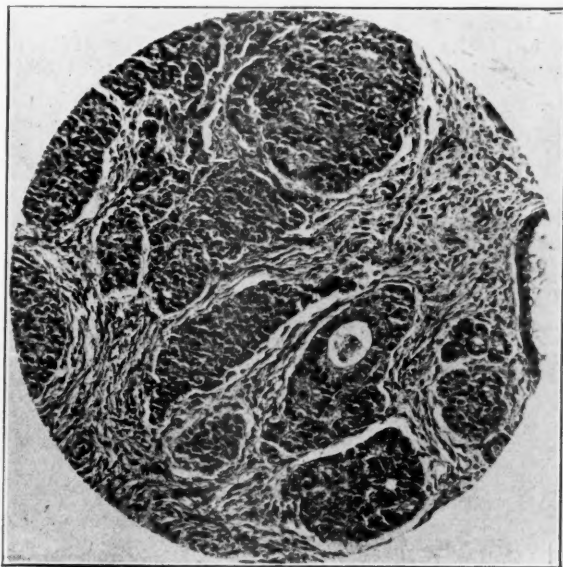


Fig. 2.—Endometrial hyperplasia, adenocarcinoma after three doses of radium 400 mg. hr. (1923, 1924, 1929), and three doses of roentgen ray (300 r in 1929, 305 r in 1933, and 600 r in 1935). ($\times 200$.)

50 mg. of radium for eight hours (400 mg. hr.) Gross findings showed uterus to be normal in size and curettings moderate in amount. Microscopic: Endometrial hyperplasia.

Fourth admission on Oct. 25, 1935. *Interval history:* For two months following the previous admission, the menstrual periods became irregular and less profuse. She then began to bleed profusely and passed large clots with the following menstrual period. In April, 1929, she received four roentgen ray treatments (300 r). The periods became irregular and the flow was scant until the latter part of 1932, when the periods became profuse and lasted from ten to twelve days. In February, 1933, the patient received two roentgen ray treatments (350 r). Bleeding diminished and the menses became irregular. This continued until the early part of 1935 when periods became profuse with passage of large clots and associated with pain. Painful menstruation was observed about one month prior to admission. Examination revealed a grossly negative pelvis. The uterus was curetted for diagnosis. Curettings were moderate in amount including a small endometrial polyp which was firm in consistency. Microscopic: Endometrial polyp with secondary adenocarcinoma (Fig. 2). The patient then received four roentgen ray treatments (600 r).

Fifth admission on Nov. 11, 1936. *Interval history:* Since discharge from the hospital, patient had no symptoms but returned for panhysterectomy. Examination revealed findings similar to previous admission. Panhysterectomy was done. Microscopic: Endometrial hyperplasia, adenomyosis, and endometrial polyp with secondary adenocarcinoma.

Since operation, the patient has been followed very carefully. She has increased in weight, feels perfectly well, and examination reveals a negative pelvis.

COMMENT

One of the most striking clinical observations in this case has been the persistence of vaginal bleeding after small repeated doses of radium and roentgen ray. The hyperplasia of endometrium has been marked. This seems to indicate that the amount of irradiation employed was not sufficient to control the factors involved in the stimulation of the endometrium and vaginal bleeding. Whether or not this is the result of excessive stimulation with estrin, it is very difficult to say. The question of repeated irradiation as a causative factor in the production of adenocarcinoma has been covered by reports of Fournier, Strachen and others who found that adenocarcinoma had existed prior to the irradiation for the supposed benign lesion.

SUMMARY

1. A case of endometrial hyperplasia with subsequent adenocarcinoma in a young girl is reported.
2. Persistent vaginal bleeding after irradiation should be thoroughly checked by repeated curettage and endometrial study.
3. Persistent hyperplasia of the endometrium after repeated irradiation should be closely followed.

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133 CLINTON STREET

DISCUSSION

DR. HOWARD C. TAYLOR, JR.—It is almost inconceivable that a carcinoma of the corpus could have as a precancerous lesion anything but a hyperplastic lesion of some type. The great question is whether we are always dealing with a single entity when we talk about endometrial hyperplasia. Ordinarily, when we use this term, we are

thinking of the hyperplasia of the menopause, or the years just before the menopause, which is associated with certain ovarian changes and possibly with a specific hormonal blood pattern. We certainly cannot say that carcinoma arises as a result of that specific type of hyperplasia. On the other hand it is probable that it arises on the basis of some local or diffuse hyperplastic changes, persisting in the menopause and perhaps developing on an entirely different basis from the classical hyperplasia.

DR. JAMES A. CORSCADEN.—Radium is an irritant, but irritants that we think of as causing carcinoma are persistent irritants. In other words, if we think of radiation as a stimulant of malignancy, we should think of it as a mild, persistent stimulant and not that which produces the acute destructive change that occurs after the application of 400 mg. hr. to any localized spot.

Statistically, the occurrence of carcinoma following radiation, irrespective of the cystic and glandular hyperplasia, is rare. We have about 1,500 cases of women treated by radiation and followed for an average period of seven and one-half years. There have occurred three cases of carcinoma of the corpus. This is probably a much smaller incidence than that among a like number of women, age for age.

AN UNUSUAL OVARIAN CYST

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REFERENCES to large ovarian cysts are not uncommon in medical literature; however, reports of enormous tumors have become rather rare because of earlier surgical interference.

The case I am reporting is of interest because of the huge size of the patient as well as the tumor and because of the adaptation of the method of treatment for her particular requirements.

Mrs. M. H., aged 38 years, was admitted to Woman's Hospital Dec. 7, 1935, complaining of swelling of the abdomen, dyspnea, and palpitation.

The patient had been well as a child. Her menses started at the age of 14. They were regular and lasted five days, until five years ago when they became irregular and a little more profuse. The last menstrual period was November 20; it was rather profuse and lasted seven days.

She had had 7 full-term pregnancies, 5 children living and well. The sixth pregnancy terminated in a placenta previa. The baby died at birth and the patient had a hemorrhage at the time of delivery. The youngest child is six years of age.

There had been a steady increase in weight for the past ten years. Three years ago she noticed that her abdomen had increased in size. Since that time her activities became increasingly limited because of pressure and shortness of breath, particularly within the past five months. For the past two months she had been confined to bed. The patient believed that the swelling of her abdomen had increased fully a third in size in the last six weeks.

She entered another hospital for treatment early in November and was sent home after a week. It was felt that nothing could be done for her.

Examination on admission revealed an extremely obese white woman, acutely ill. Her weight was 409 pounds. Temperature 100° F.; pulse 120; respirations 30, rapid and shallow. Her pulse was irregular and weak. Her abdomen was tensely distended with a large cystic tumor mass. There was a large apron of fat which extended to the knees. Hemoglobin, 79 per cent; R.B.C., 4,020,000; W.B.C., 6,450. The urine showed a trace of albumin. Nonprotein nitrogen 37.1 mg. per 100 c.c. of blood.

On December 8 an abdominal paracentesis was performed and three gallons of clear yellowish fluid were removed. The patient's pulse became rapid and rather

weak. Later her general condition improved and on December 17 another paracentesis was done, withdrawing two and one-half gallons of fluid. Her general condition improved so markedly that on Jan. 2, 1936, a laparotomy was performed. The incision was suprapubic, but above the umbilicus because of the distortion due to the heavy apron of fat. Two gallons of fluid were withdrawn from the large left ovarian cyst. The right ovary was the size of a large orange. Both ovaries were hurriedly removed and the abdomen closed. Her postoperative course was uneventful and she left the hospital Jan. 22, 1936, weighing 298 pounds.

The pathologic report was as follows: Multilocular pseudomucinous cystadenomas of ovaries (benign). (The right ovarian cyst measured 8 by 5½ by 2 cm. and the left ovarian cyst measured 23 by 8½ by 10 cm.)

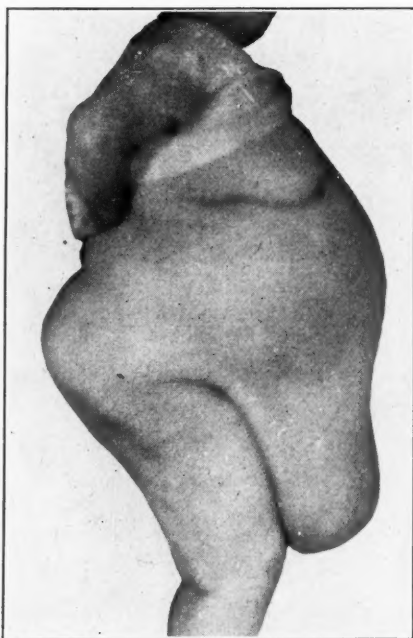


Fig. 1.

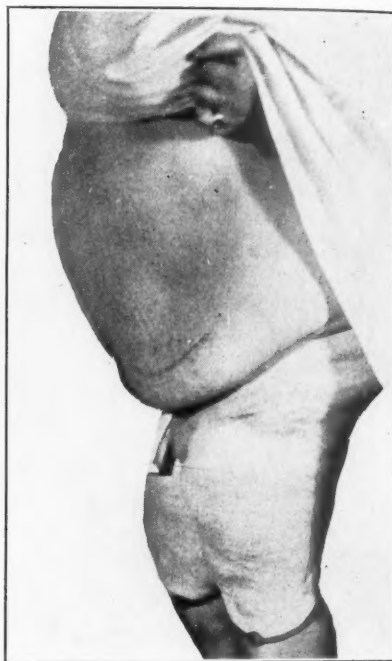


Fig. 2.

Fig. 1.—Photograph, taken shortly after admission before a paracentesis, shows enormous distention of the abdomen and large apron of fat. Weight 409 pounds.

Fig. 2.—Taken Dec. 1, 1936, after removal of the ovarian cyst and lipectomy. She weighed 284 pounds at this time.

The patient improved satisfactorily at home, but was still handicapped by the large apron of fat. She was re-admitted to the hospital April 23, 1936, for a lipectomy. A fatty panniculus, weighing 19 pounds was removed. She left the hospital April 8, 1936, weighing 284 pounds.

The patient has been active and very well since the last operation. A month after her last dismissal she went to a "talkie" for the first time in her life.

Comment.—This patient had a pituitary type of obesity as well as an enormous ovarian cyst. She was in a critical condition on admission and therefore a gradual decompression of the tumor was required. We believe this conservative or guarded procedure was the chief factor in the final satisfactory results. Immediate removal of the cysts probably would have been fatal.

GANGRENOUS VULVAR EDEMA NECESSITATING CESAREAN SECTION

RICHARD TORPIN, M.D., AND ROBERT BATTEY CRICHTON, M.D.,
AUGUSTA, GA.

MASSIVE edema of the vulva in pregnancy is quite rare, there being but ten references in the literature in the last twenty years. Usually multiple puncture, before labor is complete, allows enough collapse for delivery to take place through the vagina. However, there have been several cases reported in which the question of cesarean section is discussed.

An interesting fact is that the edema was of the labia majora while that pictured in two cases by Thorp and Wangeman was of the labia minora. In our case the inner surfaces of both labia majora became gangrenous and sloughed off, exposing the subcutaneous tissues in a craterlike ulcer which measured 2 by 10 cm. in the left labium, smaller in the right.



Fig. 1.—Photograph of vulva just prior to operation.

Case Report.—Primipara, colored, aged 23, stocky constitutional type, normal weight of 150 pounds at full-term pregnancy, admitted in labor at onset of first stage. About two weeks before, she began to have edema of feet, legs, and face. She had never attended clinic or had had any prenatal care. At about the same time she began to have headache, coinciding with sudden rapid enlargement of the abdomen. She began to have a few labor pains two days before entrance to the hospital and at the same time developed massive edema of vulva. She gave a history of fluid discharge from vagina for two days.

Physical examination of negro female in some distress, face slightly puffed, heart tones fair quality, lungs normal, abdomen very large. There appeared to be 2 fetuses with one fetal heart heard in the left upper quadrant, abdominal rate 134, another in the right lower quadrant, rate 125. One head was palpable in left

upper quadrant and there appeared to be one engaged in the inlet to the pelvis. The vulva was greatly swollen as illustrated, and there was a clear serum oozing from a rupture of skin at the lower portion of the left labium majus. Blood pressure 170/120, temperature 101° F., pulse 100, urine albumin 4-plus, white blood count 28,150, hemoglobin 65 per cent.

Notwithstanding the toxemia several consultants agreed upon cesarean section as choice of procedure. A low cervical operation was completed in thirty-five minutes with patient under cyclopropane anesthesia and delivery of female double ovum twins. Convalescence was characterized by gangrenous slough of the skin and mucosa of the inner surfaces of both labia majora. Infection of the ulceration was the cause of some fever which ranged to 102° F. for a couple of weeks. A leucocytosis was noted of 30,000 (polymorphonuclear leucocytes 85 per cent). The toxemia was treated by intravenous magnesium sulphate, glucose and free fluids, and salt-free diet. There was some anemia (R. B. C. 3,100,000) and she received one transfusion.



Fig. 2.—Photograph of vulva three days after operation showing sloughing area on each labium majus.

The gangrenous ulceration responded to dry treatment with tannic acid powder and was almost entirely healed at end of twenty days in the hospital. The edema of vulva subsided in three or four days and that of the legs and feet at the end of ten days. The infants weighing 7 pounds, 3 ounces and 6 pounds, 5 ounces, respectively, at birth, nursed and did well and left the hospital with the mother on the twentieth day.

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UNILATERAL ABSENCE OF THE FALLOPIAN TUBE AND OVARY

DANIEL R. MISHELL, M.D., NEWARK, N. J.

RECENTLY a case was observed at laparotomy in which the entire right ovary and major portion of the right tube were found to be absent. This rather unusual finding prompted a search of the literature and some very interesting facts and theories were revealed. This condition is sufficiently rare to be reported in detail.

A. M., aged 24 years, white, married one year, never pregnant, was first seen complaining of pain in the right lower abdominal quadrant. The pain was continuous, dull and aching in character, accompanied by intermittent sharp exacerbations, duration of symptoms eight months, becoming progressively worse. Eighteen months previous to the present illness the patient had an attack of severe pain in the right lower abdomen, duration one week, not accompanied by vomiting or rise in temperature, nor necessitating confinement to bed. Previous to this episode

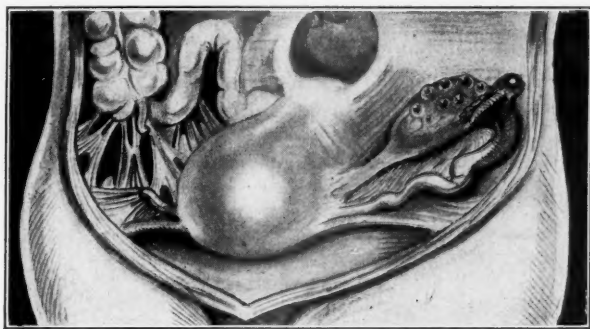


Fig. 1.—Diagrammatic sketch with uterus pulled forward and to the right showing: (1) Absence of right adnexa, (2) adhesions extending to cecum and appendix, (3) cystic left ovary.

there was no history of any abdominal pain. The menstrual history was rather interesting. Menarche occurred at the age of thirteen; the periods were regular every twenty-eight days, duration four days, normal in amount, no dysmenorrhea. During the past year the patient noticed that the periods, although regular, were decreasing in the amount of flow. During the past four months the period consisted of slight staining, duration one day. It was also noticed that the abdominal distress became more intensified just prior to the onset of the menses. The past history revealed no previous operations or severe illnesses, no marked change in weight, no history of vaginal discharge or backache.

Upon physical examination the patient seemed well-developed and nourished and in good general health. Abdominal examination revealed an area of marked tenderness over the right lower quadrant, especially pronounced over McBurney's Point. Bimanual examination showed no evidence of inflammatory changes in the vulva or vagina; the cervix was quite small and pointed upwards, the corpus rather small and retroverted. The right adnexa were not palpable; the left ovary was moderately enlarged and prolapsed in the culdesac. Urine and blood examinations were normal. The Wassermann test was negative. A gastrointestinal series was essentially negative, the appendix not visualized.

The patient was admitted to St. Mary's Hospital, Orange, N. J., for laparotomy; the preoperative diagnosis was (1) chronic appendicitis and (2) retroversion of the uterus. At operation a rather unusual picture was presented. The uterus was small and completely retroverted. The left tube appeared to be normal but the left ovary was enlarged to twice the normal size and contained numerous small cysts. A search of the right adnexal region revealed the complete absence of the right ovary and the presence of a stump of the right tube, $\frac{1}{2}$ inch long, buried in adhesions involving the broad ligament and the right parietal wall. These adhesions were rather firm in character and extended upwards to involve the cecum. The appendix was found to be only $\frac{3}{4}$ inch long, surrounded by adhesions at the ileocecal junction.

The diminutive appendix was removed, the cystic area of the left ovary resected, and the uterus suspended. The pathologic examination showed the appendix to contain polymorphonuclear leucocytes and lymphocytes scattered throughout the muscular wall. The piece of resected ovary was composed of small follicle cysts. The patient made an uneventful recovery and was discharged on the tenth post-operative day. Following the operation she was relieved of all abdominal symptoms. The menses occurred at twenty-six-day intervals, four days in duration, for the first two periods, and subsequently decreased to two and one-half days with corresponding diminution in flow.

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MEDICAL TOWER

VESICOVAGINAL FISTULA REPAIRED WITH RUSTLESS STEEL WIRE*

HENRY D. FURNISS, M.D., F.A.C.S., NEW YORK, N. Y.

CASE 1.—Woman, 24 years old, had been wearing a wishbone gold contraceptive pessary for four years. In spite of this she became pregnant in August, 1937. The pessary was removed; following this she developed a rectovaginal fistula. Evidently, one end of the pessary had become embedded in the rectovaginal septum.

She was first seen on Oct. 25, 1937, at which time a rectovaginal fistula, situated in the mid-line, at a point opposite the external cervical os of a normally positioned uterus, was found; this was $\frac{3}{4}$ cm. in the transverse, by $\frac{1}{2}$ cm. in the antero-posterior direction. On the right, there was a dense scar running from the cervix to the lateral wall of the vagina. The vagina was unusually tight. Operation was deferred because of pregnancy. She returned for operation in February, having had a midwife terminate the pregnancy in November.

Operation.—To obtain sufficient room, a left Schuchardt incision was made. With the index finger, of the doubly gloved left hand, in the rectum, the fistula was brought into view, and the scar tissue around the edges was dissected out. The rectum was then separated from the vagina. With four sutures of 00 Medrafil wire (nickel copper alloy) the rectal side of the fistula was closed, the sutures going to the mucosa, but not into the rectum. Four similar sutures were placed in the vaginal mucosa, at a right angle to the others. The Schuchardt incision was closed with catgut. Gas began to escape from the fistula on the third day, and there was fecal incontinence when the bowels moved on the fourth day. March 7, 1938, the vaginal sutures were

*Read at a meeting of the New York Obstetrical Society, March 8, 1938.

found free in the vagina; the ends had been shot with one shot. The fistula was a bit smaller than when operated upon. The deeper metal sutures could not be felt either by rectum or vagina, but were shown by x-ray picture.

She will return in two or three months for operation. Then I shall make a bilateral Schuchart incision, put a Barnes' bag in the rectum, and by traction get a better exposure, and divide the rectal sphincter completely, posteriorly, to obviate either gas or fecal pressure. I dislike the necessity of doing a preliminary colostomy.

CASE 2.—Woman aged 31 years, had a complete perineal laceration, that was sutured immediately. Healing was good except for a small portion one-half inch from the introitus, one-sixteenth of an inch in diameter. Through this there was gas and slight fecal incontinence. The ends of the sphincter ani muscle were slightly retracted, and only when the bowels were loose was there any escape through the anal orifice proper.

Operation.—The scar tissue was dissected out and the anal mucosa separated from the vaginal structures. In this way the rectum was thoroughly mobilized. The opening was then $\frac{3}{16}$ of an inch in diameter. With interrupted sutures of Medrafil No. 60 sutures, so placed that they came just short of the rectal mucosa, this was closed. These were placed in tiers, thus building up the perineum, and approximating the ends of the sphincter ani muscles. The vaginal mucosa was closed with silkworm gut sutures. Healing was uneventful. On two occasions since leaving the hospital, there has been a slight serous discharge from the skin just above the anal orifice, lasting only a few days. She has experienced complete relief. For years I have endeavored to limit the use of catgut, because of the uncertainty of its absorption time, and the wound irritation caused by it. I have found the steel wire satisfactory likewise in closing a colostomy opening, and in the closure of the rectus fascia in several suprapubic cystotomies where drainage had been employed.

54 EAST 62ND STREET

A SCISSOR TYPE CERVICAL BIOPSY PUNCH*

HARRY O. MARYAN, M.S., M.D., CHICAGO, ILL.

ADEQUATE biopsies of the cervix uteri are essential for the accurate histopathologic diagnosis. The biopsy should be large enough to include the endocervix, the cervical lip, and the portio vaginalis portion.

It is not always easy to obtain adequate-sized biopsies with scalpel or scissors, even by a skilled technique. Therefore, I have devised a simple, scissorlike cervical biopsy punch to facilitate obtaining cervical biopsies.

This (Fig. 1) consists of a pair of handles with a spring and roller attachment, a shaft with a mortise or Bruening lock, and the male and female blades. Beneath the female jaw there is attached the removable basket spring which retains the specimen. The handles are so aligned that the object is always in direct line of vision. The spurs on the handles prevent the hand from slipping when pressure is applied. The solid, upper, male cutting blade, and the lower, open, female jaw measure 16 mm. in length, 4 mm. in width, and 5 mm. in depth, and may be opened to a distance of 12.5 mm., or 0.5 inch. The male blade is invaginated into the female jaw by means of a lower shaft, slotted to insure the proper aligning of the jaws.

This punch is capable of obtaining a biopsy 12.5 mm. or thicker from a dense cervix. The maximum specimen obtained (Fig. 2) will measure 16 mm. in length, 4 mm. in width, and 12.5 mm. in depth, and will include the three areas of the cervix: the endocervix, the cervical lip, and the portio vaginalis. A specimen of any desired length up to 16 mm. can be obtained.

*Presented at a joint meeting of the Chicago Gynecological and the St. Louis Gynecological Societies, February 19, 1938, Chicago, Ill.

Made by V. Mueller and Co., Chicago, Ill.

TECHNIQUE

The full length of the male end of the punch is inserted into the cervical canal, with its female jaw on the outside. It is then maneuvered into position so that a specimen can be obtained from any desired portion of the cervix, whether it be the upper lip or the lateral sides.

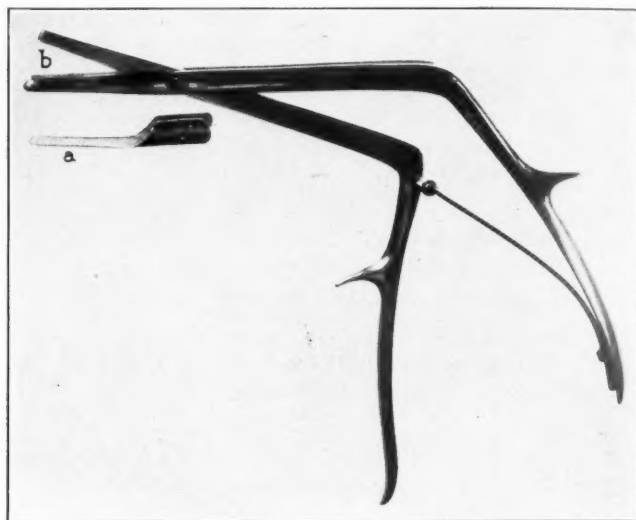


Fig. 1.—*a*, Removable basket spring; *b*, cutting jaws.

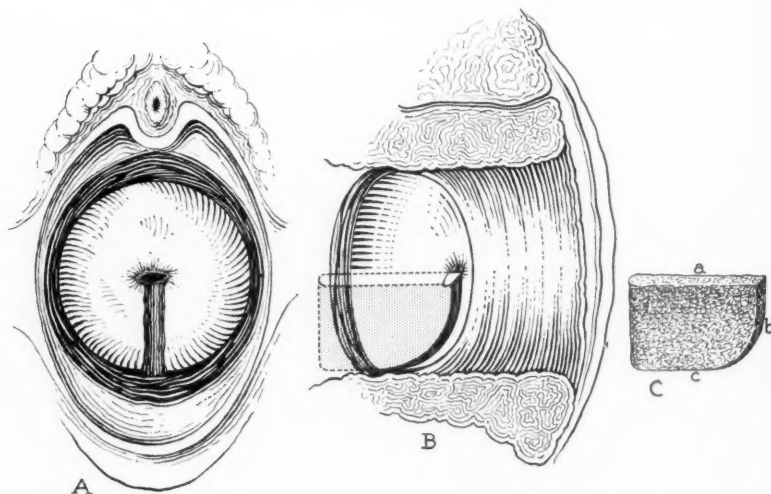


Fig. 2.—*A*, Front view, showing appearance of lower lip after biopsy. *B*, Lateral view, showing extent of biopsy from external os (*a*) toward an inward length of 16 mm. (*b*). *C*, Biopsy specimen measuring 16 mm. in length, 4 mm. in width, and 12.5 mm. in depth. *a*, Endocervix, *b*, cervical lip, *c*, portio vaginalis.

By means of a firm, forceful momentary pressure, and then by a sudden, more forceful pressure to the blades, the specimen is cut and forced into the spring basket. By sliding the basket off the lower jaw when the handles are extended, the specimen is simply removed. Should the specimen remain in the lower jaw, it can be pushed out with the thin end of the spring basket.

Editorial

Syphilis and Pregnancy

THE world has become roused to the significance of syphilis in our social structure. A more or less insidious infection, its consequences well known, effective treatment a matter of common knowledge, yet we have hesitated to attack it in an open manner. The medical profession has been acquainted for a long time with the deplorable results of unrecognized and untreated manifestations of this world-wide affliction. Progress in its handling received a great impetus in recent times by the outstanding discoveries of Wassermann and Ehrlich, and their co-workers and successors. Yet evidently, publicity was necessary in order to disseminate this valuable technical knowledge and apparently this is now being accomplished. Governmental agencies have come to the assistance of the medical profession both here and abroad. An aroused public interest has stimulated legislative enactments such as the laws recently placed on the statute books by New York and other states, calling for premarital examinations and serologic tests in pregnancy.

The responsibility for carrying out these measures and their interpretation rests upon the doctor and he must prepare himself accordingly. How well is he equipped to do this? In other words, to eradicate congenital syphilis with its attendant loss of life and the physical disabilities which develop in those infants who survive. The diagnosis of the disease in prospective parents and its adequate treatment are of equal importance.

Since the highest attack rate occurs between the sixteenth and thirty years of life, which corresponds in a measure with the active childbearing period, the incidence of syphilis in the pregnant woman is a problem which merits attention. Most well conducted hospital clinics have for many years carried out serologic tests in their patients but the clientele of the private physician has not been subjected to similar methods of diagnosis. The legal measures now being introduced will enforce upon all pregnant women the serologic tests. In a minority, certain clinical manifestations of the disease may be manifest but a physician must familiarize himself with these so that, if present, they may be recognized. Serologic tests, as a matter of fact, are of no aid in the early stage of the primary lesion and in many instances of the later stages. The innocuous erosive chancre of the cervix requires dark-field studies for confirmation. It has been found that the great majority of syphilitic prenatal patients are clinically latent and that a significant history can be obtained in less than half. This shows the need for routine serologic tests. Positive reactions may occur in nonsyphilitic

patients, such as those who suffer from yaws, leprosy, malaria, and relapsing fever, but a pseudopositive result due to pregnancy itself has not been definitely substantiated. An apparent problem is the detection of the syphilitic prenatal patient who gives a single negative Wassermann reaction and goes through pregnancy undiscovered, yet gives birth to a frankly infected infant. Different modifications of the Wassermann test have yielded variable results. There is need therefore for the universal adoption of a technique of proved value by laboratories and this must be brought about in all communities by cooperation between the groups immediately concerned. As another means of identification the more sensitive precipitation and flocculation tests can be used as confirmatory measures. Instances are known of cases in which the Wassermann test was consistently negative and the precipitation test positive, with the converse likewise true. A routine combination of these diagnostic agencies must be developed in order that the greatest number of latent syphilitic prenatal patients may be detected. Where discrepancies in both tests exist or where equivocal results are obtained, a thorough inventory is essential, which should include the repetition of the tests as well as a thorough scrutiny for significant data in the previous history of the patient. This may need to be extended to the husband and other children.

That pregnancy itself has an inhibitory and protective effect on syphilis has been contended by many authorities. It is unfortunate that up to the present time no test has been devised which is absolutely specific and completely sensitive, and there may be infrequent instances of completely negative results in prenatal patients who are undoubtedly syphilitic. Here, a carefully taken history and clinical manifestations irrespective of serologic findings may serve to detect some of these unusual cases. Again, where the disease is suspected serologic examinations repeated at short intervals may subsequently yield a positive result.

It is quite evident that inadequacies, no matter how rare, demand further standardization of processes and procedures and these should be, as already stated, the task of the agencies concerned. It has been shown very definitely that where the diagnosis of syphilis has been established not later than the fifth month of pregnancy efficient treatment will prevent the transmission of the disease from mother to offspring in approximately 95 per cent of the cases. Enough is known of such successful methods of treatment to assure the eradication of congenital syphilis in practically all instances and to make of the transmitted type of the disease a medical rarity. Again, it is the task of the medical man who undertakes the care of pregnant women to assume responsibility and to qualify himself accordingly, because the precautionary legislation already adopted by certain states will undoubtedly be invoked by others within a short time. The fight against syphilis should constitute one of the most important present-day aims of preventive medicine.

—*M. D. Speiser.*

Society Transactions

NEW YORK OBSTETRICAL SOCIETY

MEETING OF JANUARY 11, 1938

Endometrial Hyperplasia (Puberty) Adenocarcinoma, Fifteen Years' Follow-Up. Case Report. Dr. Vincent P. Mazzola. (For original article, see page 698.)

Congenital Absence and Traumatic Obliteration of the Vagina and Its Treatment with Inlaying Thiersch Grafts. Dr. Virgil S. Counsellor, Rochester, Minn. (By invitation.) (For original article, see page 632.)

The Persistence of Gonococcal Infection in the Adnexa. Drs. W. E. Studdiford, W. A. Casper, and E. M. Seadron.

The Dilating Bag in Obstetrics. Dr. Edward G. Waters. (For original article, see page 639.)

MEETING OF FEBRUARY 8, 1938

The following papers were presented:

The Diet of the Pregnant Woman. Dr. E. V. McCollum, of Baltimore, Md. (read by invitation). (For original article, see page 586.)

Fetal Respiration and Its Bearing Upon Injuries of the Newborn. Dr. Franklin F. Snyder, of Baltimore, Md. (by invitation).

MEETING OF MARCH 8, 1938

The following papers were presented:

Vesicovaginal Fistula Repaired With Rustless Steel Wire. Case report by Dr. H. D. Furniss. (For original article, see page 706.)

Some Present Day Problems in Syphilis and Pregnancy. Dr. J. R. McCord, of Atlanta, Ga., by invitation.

Vesicovaginal Fistula After Complete Abdominal Hysterectomy. Dr. Albert H. Aldridge.

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF FEBRUARY 3, 1938

The following paper was presented:

Carcinoma of the Cervix. Dr. Norman F. Miller and Dr. Clair E. Folsome. (For original article, see page 545.)

CHICAGO GYNECOLOGICAL SOCIETY

JOINT MEETING WITH THE ST. LOUIS GYNECOLOGICAL SOCIETY

MEETING OF FEBRUARY 19, 1938

The following papers were presented:

A Scissor Type Cervical Biopsy Punch. Dr. Harry O. Maryan. (For original article, see page 707.)

Cesarean Section—An Analysis and a Discussion. Dr. Wm. C. Stude.

Results of Cultures of the Uterus at Cesarean Section. Dr. T. K. Brown.

Etiology of Cervicitis. Dr. Melvin A. Roblee. (For original article, see page 1039, June, 1938, issue.)

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF MARCH 18, 1938

The following papers and discussions were presented:

Rhythmic Changes in the Skin Capillaries and Their Relation to Menstruation. Dr. John I. Brewer. (For original article, see page 597.)

Unpredictability of the Phenomena Accompanying the Menstrual Cycle in Normal Women. Drs. Julius E. Lackner, Hans Wachtel, and Samuel Soskin. (For original article, see page 612.)

Large Degenerated Subserous Myoma. Dr. Irving F. Stein.

WASHINGTON GYNECOLOGICAL SOCIETY

MEETING OF NOVEMBER 27, 1937

The following papers and discussions were presented:

The Use of Vitamin E in the Management of Repeated and Threatened Abortions. Dr. J. Keith Cromer.

The Relative Value of Pure Oxygen and of Carbon Dioxide Mixtures in Experimental Resuscitation. Drs. N. J. Eastman, R. B. Dunn and Joseph Kreiselman. (For original article, see page 571.)

NEW ORLEANS GYNECOLOGICAL AND
OBSTETRICAL SOCIETY

MEETING OF JANUARY 21, 1938

The following papers were presented:

The Elliott Treatment of Pelvic Inflammatory Diseases of Women as Used in the Office of Private Practice. Dr. Earl C. Smith.

Ruptured Hemorrhagic Ovarian Follicle Complicating Acute Appendicitis. Dr. L. A. LeDoux.

MEETING OF APRIL 21, 1938

The following paper was presented:

Granulosa Cell Tumor of the Ovary. Dr. Eugene H. Countiss. (For original article, see page 680.)

Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

Review of New Books

Obstetrics

This volume on *The Heart in Pregnancy*¹ by Jensen is an outstanding discussion both from the standpoint of cardiology and obstetrics. The range of topics is quite comprehensive, and an analysis of each factor is so detailed that the book is unusually complete, and must be regarded as a volume of especial value. The work represents an intensive study of the heart cases complicated by pregnancy seen in the St. Louis Maternity Hospital over a period of eight years, and in addition covers such a wide range of the literature that the bibliography comprises twenty-six pages of references.

Dr. Jensen divides his book into three parts: the effect of pregnancy on the normal heart; abnormal cardiac impulse formation during childbearing; and organic heart disease and pregnancy. The subdivision of these various headings brings up a study on the increase of cardiac work during pregnancy. Here Jensen regards two facts as standing out among all the evidence, namely: that in pregnancy the increase in metabolism may well be the cause of cardiac overwork and that the volume of the circulating blood is increased often out of proportion to the increase in weight. All factors which have largely been assumed to increase the work of the heart during pregnancy have been fully considered. In regard to the mechanism whereby the heart meets these increased demands, he discusses increased peripheral resistance, the pulse, the cardiac output in pregnancy, oxygen utilization, and circulation time. The author feels that there is a regrettable inconsistency in opinions expressed about most of these subjects and regards them as a fertile field for future researches.

The physiology of the normal heart during normal pregnancy opens with a discussion of the long dispute over the tendency of the heart to increase in size in pregnancy, continues with the roentgen examination of the heart and the electrocardiogram as a means of examination. He notes that the electrocardiogram undergoes changes suggestive of various axis deviations but the irregularity with which the heart is displaced precludes any regular occurrence or sequence of the variations reported.

In a short second part of the book the author discusses the abnormal cardiac impulse formation during pregnancy, taking up tachycardia, bradycardia, extrasystoles and auricular flutter and heart block. As his personal experience he believes there is a slowing of the puerperal pulse as compared to that in pregnancy, a return to normal from the increased pulse rate incidental to pregnancy, with a prevailing basal rest level of the pulse rate.

In the third part of the book Jensen discusses rheumatic heart disease and pregnancy. Commenting on the statistics of rheumatic disease, and the incidence of rheumatic heart disease and pregnancy, he notes that the recorded death rate gradually has been reduced from 8 to 10 per cent to near 2 per cent, and the average death rate in a large series of cases is 4.3 per cent. He notes that heart disease ranks among the four or five most important causes of maternal death. For prog-

¹*The Heart in Pregnancy.* By Julius Jensen, Assistant Professor of Clinical Medicine, Washington University School of Medicine, etc. 371 pages. The C. V. Mosby Company, St. Louis, 1938.

nosis he considers the functional capacity of the heart as one of the best indices, and has grouped his cases according to the classification of the American Heart Association.

There is a thorough discussion of congestive heart failure, and he feels that a death rate from 2 to 3 per cent among gravidocardiacs appears irreducible at the present time. Congestive heart failure he states is a factor in 70 per cent of the cases fatal from this complication. The material he has worked over indicates that the prognosis in heart disease during pregnancy grows worse with advancing age, although it does not exceed what might have been expected among women without heart disease, and he states that there is no evidence that pregnancy as such has increased this death rate.

The effects of various cardiac lesions on prognosis are fully described. The author discusses the various factors offered to show that childbearing influences the rheumatic heart or pathologic processes in the heart, and presents his own ideas as to the onset and development of congestive failure. The various complications of valvular heart disease during pregnancy from his own experience and from the literature are discussed, with an analysis of the different views held.

There is a splendid chapter on the management of pregnancy and rheumatic heart disease, and the author ascribes credit to improved prenatal care for the reduction in the death rate. He considers as an indication for the interruption of pregnancy heart failure which does not respond to treatment. Various methods of delivery of cardiac patients are presented with statistical reviews from the literature, and the summary is quite in accord with the conservative attitude of most American clinics, especially as regards cesarean section and sterilization. In discussing the various types of anesthetics and analgesic agents, he properly states that the choice depends upon individual preference and individual study of the patients. The following chapters of this volume discuss the nonrheumatic heart diseases such as bacterial endocarditis, cardiovascular syphilis, congenital heart disease, degenerative heart disease, kyphoscoliotic disease and thyroid heart disease. Of particular interest in the chapter on degenerative heart disease is the manner in which the author has developed the recent views regarding the interrelationship of the increase of blood pressure in toxemia, essential hypertension and cardiovascular disease, a subject in which he and his associates have independently come to quite similar conclusions with those which Herrick has propounded.

This volume is so all inclusive of the various phases of the subject, so fully documented and moot points in the literature are so thoroughly analyzed, that it should be useful as a working manual as well as a source of reference to all cardiologists and obstetricians.

—Philip F. Williams.

The contributions from this well-known French clinic of the year 1937 appear under the title of *Leçons du Jeudi Soir à la Clinique Tarnier*.² Fifteen contributions are published in this volume, and they may be considered, in so far as clinical practice is concerned, as expressing the present views of this French School. Brindeau, the chief of the clinic, opens the volume with a history of cesarean section. He concludes that the cervical segment operation permits a trial of labor and will supersede hysterectomies or the operation of Portes in many instances. Metzger discusses the third stage of labor, and counsels conservatism. Lanteujoul discusses pregnancy complicated with myoma, and concludes that indications for operation are extremely limited, and during pregnancy or labor he insists only on myomectomies. He states that, on the contrary, during the puerperium, it is the attitude of the clinic to have recourse to hysterectomy.

Suzor describes the treatment of toxemia and Hauch recounts their experiences in various trials of analgesia and obstetric narcosis. The use of obstetric analgesia has been increased in their clinic in five years to from 50 to 70 per cent of the women. There has been almost an equal increase in the use of inhalation anesthesia with the use of barbiturates or agents of like nature. Hauch concludes that they have

²*Leçons du Jeudi Soir à la Clinique Tarnier*. Published under the direction of A. Brindeau. One volume, 318 pages, 66 figures. Vigot Frères, Paris, 1938.

as yet not discovered a satisfactory analgesic agent. The social aspect of obstetrics is discussed by Vandescal who analyzes the maternity benefits given in France and other countries of the world. Among the other topics discussed may be mentioned rupture of the uterus, comparative merits of forceps and version, obstetric shock, syphilitic lesions in the newborn child.

As usual this volume of finely prepared material reflects the excellency of the work performed in this obstetric center.

—Philip F. Williams.

Only two years have elapsed since publication of the preceding edition of this *Synopsis of Obstetrics and Gynaecology*³ by Bourne but progress in these two fields of late has been rapid. This latest edition has been thoroughly revised and brought up to date as evidenced, e.g., by inclusion of discussions of mandelic acid and prontosil.

The systematic and remarkably comprehensive presentation of an immense amount of material in precise and consistently clear language, aided by excellent diagrammatic sketches at the bottom of the page, has been duly emphasized in reviews of preceding editions. Both advice and warning always are offered in the form of terse statements.

The American reader will discover but few points not entirely in agreement with our common practice, as for instance, giving an enema immediately before forceps extraction, the instrument being applied with patient lying on her side. The author exhibits noteworthy conservative views in regard to the value of organotherapy in gynecologic practice.

This little volume can unreservedly be recommended to student and practitioner.

—Hugo Ehrenfest.

This most exhaustive discussion of the *Diseases of Pregnant Women*⁴ by Henri Vignes is presented in form of monographs. We had occasion to describe in this JOURNAL the two preceding volumes of this series, dealing respectively with (1) Disorders of the Digestive Tract, and (2) Diseases of Liver and Pancreas, and Disorders of Nutrition, etc.

This third monograph is devoted to the *Affections of the Skin*. We can only repeat what we have stated before, namely, that the familiarity of the author with existing literature is amazing. Every known effect of pregnancy on either the physiology or pathology of the skin, obviously including hair and nails, is thoroughly discussed from the viewpoint not only of etiology and symptomatology but also of therapy.

As pointed out in previous reviews, the underlying arrangement of this truly encyclopedic presentation (according to the different organs of the body) obliges consideration of subjects such as lepra, erysipelas, and puerperal scarlatina. However, a carefully prepared index easily overcomes this inevitable shortcoming of the underlying scheme.

This valuable addition to obstetric literature can be qualified as incomparable, simply because no similar book of ready reference has ever been published in any language.

—Hugo Ehrenfest.

Eden-Holland's *Manual of Obstetrics*,⁵ first published in 1906, requires neither description nor recommendation. It seems, however, worth noting that this new

³*Synopsis of Obstetrics and Gynaecology*. By Aleck W. Bourne, Consulting Obstetric Surgeon, Queen Charlotte's Hospital, etc. Edition 7, fully revised with numerous diagrams, 452 pages. William Wood and Company, Baltimore, 1937.

⁴*Maladies des femmes enceintes*. Vol. III. Affections de la peau. By Henri Vignes, with collaboration of F. Hanoun and G. Vial. 202 pages. Masson & Cie, éditeurs, Paris, 1937.

⁵*A Manual of Obstetrics*. By Thomas Watts Eden, Consulting Obstetric Physician to Charing Cross Hospital, etc., and Eardley Holland, Obstetrical and Gynaecological Surgeon, and Lecturer on Obstetrics and Gynaecology, the London Hospital, etc. Edition 8, with 12 plates and 398 illustrations, 765 pages. J. & A. Churchill, Ltd., London, 1937.

eighth edition has been most thoroughly revised, a task requiring a good deal of rearranging and the rewriting of several sections. Holland may well be proud of the fact that in spite of inclusion of all the more recent developments in obstetric science and of the addition of many new illustrations and three color plates, the book has grown by only fifteen pages. Thus it remains a manual in the true meaning of the word, ready at hand for any desired information which it supplies in the exact and succinct language of the text, by means of excellent illustrations and as well in form of brief abstracts of correlated literature, appended as Guide to Further Reading at the end of each of the nine sections.

That this volume actually has been brought up to date is rather convincingly demonstrated by the authentic evaluation of prontosil in obstetric practice and the favorable consideration of the classification of pelves as elaborated by Caldwell and Moloy.

—Hugo Ehrenfest.

In a series of monographs, explicitly designed for the benefit (Fortbildung) of practitioners, as volume 24, is presented this complete summary of available information concerning the *Rôle of Vitamines (especially A and C) in Pregnancy*.⁶ Its author, Gerhard Gaetgens, is particularly competent to prepare such a summary because our present knowledge in this respect to a great extent must be credited to his own investigations. In a brief résumé of the contents of this work he emphasizes the fact that clinical and experimental experience proves that there exists an indivisible biologic complex between pregnancy and the puerperium. In the maternal systemic changes in both phases, the purposeful adaptation to the needs of the child is evident. This is brought about by vegetative and hormonal regulation as well as by various vitamins. Among them Gaetgens discusses in detail vitamins A and C, fully aware that further research is required in regard to others of the vitamins.

In this monograph the obstetrician will find much new information, in part of great practical importance.

—Hugo Ehrenfest.

Arnoldo de Moraes' Manual, *Propedeutica obstetrica*,⁷ of Obstetrics has reached its fifth edition since 1924. It is particularly aimed to fill the wants of practitioners and students and therefore emphasizes those interventions which do not fall into specialistic hands. As elsewhere, throughout South America, increasing interest is shown in prenatal care. The format, illustrations and text conform to previous editions. The book is well planned, sufficiently detailed, and is evidently a favorite.

—R. T. Frank.

Pre- and Postnatal Care

These *Collected Studies on the Dionne Quintuplets*⁸ represent the cooperative work of nine staff members of the St. George's School for Children Study of the University of Toronto. The six separate studies, combined in this volume, deal respectively with biology, mental growth, early social development, development of self-discipline, routine training, and early development in spoken language of these remarkable quintuplets.

Of particular interest to the obstetrician is the exhaustive biologic study made by John W. MacArthur and Norma Ford, which leads them to the definite con-

⁶*Der Vitaminhaushalt in der Schwangerschaft mit besonderer Berücksichtigung der Vitamine A und C.* By Dr. Med. Gerhard Gaetgens, Universitätsfrauenklinik zu Leipzig. With 21 illustrations, 161 pages. Published by Theodor Steinkopff, Dresden, 1937.

⁷*Propedeutica obstetrica.* Prof. Arnoldo de Moraes, Professor Cathedrático de Clinica Gynecologica da Faculdade Nacional de Medicina da Universidade do Brasil. Edition 5, with 490 pages, 158 illustrations. Grafica Suer, Rio de Janeiro, 1937.

⁸*Collected Studies on the Dionne Quintuplets.* By W. E. Blatz, N. Chant, M. W. Charles, M. I. Fletcher, N. H. C. Ford, A. L. Harris, J. W. MacArthur, M. Mason, and D. A. Millichamp. Illustrated. The University of Toronto Press, Toronto, 1937.

clusion that the Dionne quintuplets are a set composed entirely of identicals, derived from a single ovum. They are of the same sex, have all the same blood group (O), and are nearly indistinguishable in eye color, hair color, texture, and form, and in degree of skin pigmentation. There is a striking likeness of the finger, palm, and sole prints. Any pair of them are as alike as identical twins. A detail in the history suggests the early abortion of a sixth embryo, whose survival might have bridged a noticeable gap between Annette and Emilie.

Some 60 other cases of quintuplet births were traced in medical literature. The Dionne quintuplets, however, are unique as having survived as an unbroken set, an achievement made possible by the practice of modern pediatrics and the untiring efforts of their attending physician, Dr. Allan Roy Dafoe, and his aides.

It is planned to extend these studies in other essential ways as the children grow older.

—Hugo Ehrenfest.

After a lapse of six years the authors present the fifth edition on, *The Management of the Sick Infant and Child*,⁹ thoroughly revised to include the many advances in this specialty. The subject matter is divided into three parts. The first deals with such general considerations of the subject as vomiting, diarrhea, nutrition, hemorrhage, convulsions, fever and prematurity; the second part discusses regional and infectious diseases, behavior problems, allergy and disorders of internal secretion; while the third part describes methods and techniques of treatment, formulas and prescriptions for diets for normal and abnormal conditions. The section on drugs includes a consideration of dosages and a collection of prescriptions which arose in the author's private practice or the children's wards of various hospitals.

Of particular interest to obstetricians should be the consideration of the subject of intracranial hemorrhage, the ideas presented on the topic of prematurity, skin diseases of the newborn, vulvo-vaginitis, dysfunctions of the various glands of internal secretion and syphilis. There are many points discussed under methods of treatment which are germane to the practice of obstetrics, if the obstetrician retains the care of the newborn. It is interesting to note that the authors are cautious in their recommendations for the use of sulfanilamide for disorders of the sick infant.

—Philip F. Williams.

The importance of prenatal care and the significance of care after birth are emphasized in this small book, *Prenatal and Postnatal Management*,¹⁰ which is an excellent manual on preventive medicine in obstetrics. Dr. Wilson gives an excellent system for history, examination, and management of normal pregnancy, and then proceeds to what might well be termed prenatal study of abnormal pregnancy. Under placenta previa he mentions amniography and cystography as aids in diagnosis of placenta previa. Both methods are considered of questionable value in this country. He gives a concise consideration of local maternal conditions which are likely to affect parturition in discussing malformations of the soft parts as well as those of the bony pelvis.

The various systems are reviewed in a chapter on the general maternal conditions affecting pregnancy. The author does not feel that induction of premature labor is in place in heart disease. He emphasizes the need for a complete hemogram in pregnancy. For the various infections of the urinary tract the author recommends mandelic acid and ammonium citrate in pregnancy, reserving in-dwelling catheters for extremely persistent cases. In discussing the endocrine system he states that ovarian deficiency may be the cause of primary uterine inertia in labor, and suggests studies and treatment during pregnancy to avoid consequent inertia.

⁹*Management of the Sick Infant and Child*. By Langley Porter, Dean, University of California Medical School, and Professor of Medicine, etc., and William E. Carter, Director, University of California Hospital, Out-patient Department, etc. Edition 5, revised, illustrated, 874 pages. The C. V. Mosby Company, St. Louis, 1938.

¹⁰*Prenatal and Postnatal Management*. By J. St. George Wilson, Hon. Obstetric and Gynaecological Surgeon, Royal Infirmary, Liverpool, etc. With a foreword by Sir Comyns Berkeley. With 80 figures and a color plate, 206 pages. William Wood & Co., Baltimore, 1937.

Toxemias of pregnancy are divided into six groups. It is evident that the Liverpool Clinic practices very conservative therapy in these conditions. Suggestions are made as to diagnosis of the diseases of the products of conception and some extremely well executed roentgenographs of abnormal fetuses are found here.

In discussing venereal diseases in pregnancy, the author remarks that the treatment of syphilis in pregnancy is designed to prevent infection of the fetus and not necessarily to cure the mother. He recommends alternating series of injections of arsenic and bismuth.

There is ample discussion of the conditions which demand the induction of labor and the methods of these procedures.

The use of the x-ray in antenatal management forms the subject matter of a small, concise chapter, although the subject of pelvic and fetal mensuration is studied rather briefly. The author does not hesitate to express his opinions on contraception and sterilization and gives full consideration of the indications and methods of both.

The subject of care during convalescence after childbirth is extremely well handled. He regards the management as being divisible into prophylactic and active methods. The prophylactic methods include those previously discussed in the antenatal periods and a succinct summary of intrapartum care. In this section there is a series of illustrations picturing exercises of various types to restore body tone.

This is an excellent though brief discussion of prenatal study and postnatal management.

—Philip F. Williams.

*The Baby's First Two Years*¹¹ is a book intended as a guide to young mothers. It discusses the surroundings of the child, its growth and development, with instructions for hygiene and nutrition, and a short discussion of the more common complaints to which the child in infancy may be subject.

There is an excellent chapter on a typical day from a child's life which should do much toward training the young mother to a definite routine. The book closes with various records and recipes which should be of help. The photographic illustrations add much to the value of the book. One can well recommend this book to recent obstetric patients.

—Philip F. Williams.

Gynecology

Dr. Titus has written a very fine monograph, *Diseases of Women*,¹² to meet the gynecologic problems of the general practitioner. The subject matter, presented simply and concisely, stresses the need of early and accurate diagnosis. He has gone into particular detail regarding the office treatment of such gynecologic conditions as may be handled in ambulatory patients. The text follows a standard classification of arrangement discussing by organs, the infections, tumors, and displacements to which they are subject. The nonoperative handling of retrodisplacements of the uterus and use of pessaries is fully considered. In discussing ectopic pregnancy he suggests colpopuncture by needle and syringe, a method which should only be used if preparation for abdominal operation is present. He emphasizes the need for transfusion in these cases. The author wisely cautions against the indiscriminate administration of the various glandular substances in his excellent consideration of hormonal disturbances. He offers the general practitioner a working schedule of the essential steps necessary in studying sterility, and points out the

¹¹*The Baby's First Two Years*. By Richard M. Smith, Assistant Professor of Pediatrics and Child Hygiene, Harvard Medical School and School of Public Health, etc. With illustrations, 121 pages. New and revised edition. Houghton Mifflin Company, Boston, 1937.

¹²*Diseases of Women*, for the General Practitioner. By Paul Titus, M.D., Obstetrician and Gynecologist to the St. Margaret Memorial Hospital, Pittsburgh, etc. Edited by Morris Fishbein, M.D. Illustrated, 320 pages. National Medical Book Co., Inc., New York, 1937.

necessity for such conditions to be handled by a group rather than by one man. Of particular benefit to the gynecologic patient whose preparatory and postoperative care must be handled by the general practitioner, are the two final chapters on these subjects; they contain instruction which is frequently lacking in the care of such patients.

The book is highly recommended to the general practitioner whose practice includes the care of women with gynecologic ailments.

—Philip F. Williams.

The fifth edition of this well-known classic, *Operative Gynecology*,¹³ has been entirely revised and reset. It appears six years after the previous edition. In addition to the two Crossens, a chapter on the Intestinal Tract in Relation to Gynecologic Surgery and a chapter on Anesthesia in Gynecologic Surgery were written by Dr. H. S. Brookes, Jr. Two hundred new illustrations have been added, now numbering twelve hundred and sixty-four.

In the main, the same methods of approach which have made this book so valuable, have been maintained, the questions posed being whether operation is needed, if so what operation should be selected, and finally, the treatment before and after operation. This volume is by far the most complete and comprehensive one in existence on operative technic in gynecologic surgery. It has proved so valuable because no details have been neglected and therefore either the occasional operator or the gynecologist can, without trouble, find all necessary directions concerning the choice and execution of an operation within its pages. Included also is collateral information such as the details of radium and radiation treatment.

The contents are so huge that no attempt at detailed review can be undertaken. Suffice it to say that I have been able to find a large number of operations selected at random. The authors do not hesitate to indicate their preferences but on the other hand do not slur such operative techniques as they themselves probably do not utilize. In a book strictly confined to surgical techniques the chapter on nervous and mental symptoms in relation to gynecologic surgery is particularly apt and valuable. This book, as heretofore, can be most heartily recommended to the profession.

—R. T. Frank.

The abstracts and discussions of papers presented at the First International Conference on Fever Therapy in New York City in 1937 are presented in this volume, *Fever Therapy*,¹⁴ which has been edited by the members of the American Committee.

The subject matter offers in English, French, and German discussions on the subject of fever therapy from many standpoints. The opening section deals with the physiology and pathology of this mode of treatment. The complications and reactions to the therapy, and preparation of patients for such therapy are presented. Fever therapy of such miscellaneous diseases as cardiovascular disease, acute rheumatic fever and dengue are subsequently discussed. The employment of the method in ocular disturbances, neurology and psychology and other systemic disease is then taken up. A symposium of eight papers deals with the subject of the treatment of syphilis by fever therapy.

Of particular interest to the gynecologist is the symposium of twelve papers discussing fever therapy of gonococcal infections. Bierman and Horowitz contribute an article on the treatment of gonorrhea of women by means of the combined systemic and additional local heat. They state that the average number of treatments necessary to eradicate the gonococci from their last series of cases was 1.4 per

¹³**Operative Gynecology.** By Harry Sturgeon Crossen, Professor Emeritus of Clinical Gynecology and Obstetrics, and Robert James Crossen, Assistant Professor of Clinical Gynecology and Obstetrics, Washington University School of Medicine, etc. Edition 5, entirely revised and reset. With 1264 illustrations including three color plates, and 1076 pages. The C. V. Mosby Company, St. Louis, 1938.

¹⁴**Fever Therapy.** Abstracts and discussions of papers presented at the First International Conference on Fever Therapy, March 29-31, 1937. College of Physicians and Surgeons, Columbia University, New York, 486 pages. Paul B. Hoeber, Inc., New York, 1938.

patient, and conclude that the outlook for the woman with gonorrhea has been very much brightened by the development of the combined heating procedures described.

—Philip F. Williams.

Bonnet has presented for his French colleagues a very clear description of the Rubin test under the title of *Insufflation tubaire kymographique*,¹⁵ to which both Professor Faure and Dr. Rubin have added forewords. He has made certain minor modifications of the Rubin apparatus and has constantly employed the kymograph to obtain graphic records of his results. The graphs are quite similar to those first published by Rubin and his explanations are based on conclusions which Rubin has popularized. He discusses the physiology of the tubes and ovaries in relation to the test, especially, in regard to x-ray stimulation of the ovarian function and its relation to the peristaltic movements of the tube.

From the standpoint of therapy he has found that 20 per cent of his patients with tubal spasm became pregnant after treatment, and 21 per cent of his patients with altered patency became pregnant after repeated treatments. He discusses this method in contrast to such other forms of treatment as salpingostomy and the use of lipiodol.

—Philip F. Williams.

Miscellaneous

In his book on *Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases*,¹⁶ Dr. Young has given a fundamental study of the greatest importance. There are introductory chapters on the history of hermaphroditism and its embryology. On the latter he had the advice of Streeter and Hartman, and standard sources have been freely used.

The main chapters are on personal cases described in detail. There are six cases of male pseudohermaphroditism, five of which had vaginas opening into the urethra. Four female pseudohermaphrodites showed enlargement of the adrenal cortex, large clitoris, and persistent urogenital sinus. There are three cases in which in young girls the adrenals were resected. Of these only one showed an increase in estrogenic substance in the urine. A number of unusual "practicing" hermaphrodites are described and one true hermaphrodite is recorded together with the literature of twenty cases.

An adrenal tumor in a patient suffering from the adrenogenital syndrome was successfully removed. Ovarian growths with masculinization, prostate in female pseudohermaphroditism, hyper- and hypogenitalism, as well as gynecomastia are dealt with. The subject of hypospadias, epispadias, cryptorchidism and atresia ani are fully discussed. The final chapter might be called an endocrine summary.

This book is not only valuable because of the large amount of case material but likewise for the minute and beautifully illustrated operative technique (drawn by Didusch) used in the treatment of these numerous cases. A full description of the simultaneous posterior exposure of both adrenals devised by Young is included. Everyone interested in any of the subjects dealt with should consult this important volume.

—R. T. Frank.

*The Adrenal Cortex and Intersexuality*¹⁷ is a symposium in which a number of different specialists have combined. The foreword is by Sir Walter Langdon-Brown

¹⁵*Insufflation tubaire kymographique par la méthode de Rubin.* By Louis Bonnet, ancien chef de clinique gynécologique à la Faculté de Médecine de Paris. Illustrated: 96 pages. G. Doin & Cie, Paris, 1937.

¹⁶*Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases.* By Hugh Hampton Young, Professor of Urology, Johns Hopkins University, etc. With 379 plates containing 534 drawings by William P. Didusch; 649 pages. Williams and Wilkins Company, Baltimore, 1937.

¹⁷*The Adrenal Cortex and Intersexuality.* By L. R. Broster, Clifford Allen, H. W. C. Vines, Jocelyn Patterson, Alan W. Greenwood, G. F. Marrian, and G. C. Butler. With a foreword by Sir Walter Langdon-Brown. Illustrated, 245 pages. Chapman & Hall, Ltd., London, 1938.

of the University of Cambridge. The clinical study of the adrenogenital syndrome has been dealt with clinically and surgically by Broster; the psychologic by Clifford Allen. A scientific study of this syndrome includes the histologic observation by Vines and biochemical ones by Jocelyn Patterson as well as Marrian of Toronto.

The book contains a wonderful amount of clinical material. The surgical results following adrenalectomy are remarkably good (33 adrenalectomies with but one death), and yet the book as a whole is extremely disappointing. This is due to the fact that particularly in the clinical chapter the work-up is frequently defective and the conception of what actually constitutes a clear-cut adrenogenital syndrome is beclouded by the fact that a number of doubtful and merely allied conditions are included. The follow-up likewise is frequently insufficient and criteria loosely drawn. The surgical approach has been changed. In his earlier publication Broster used the transthoracic route. He has now changed to the lumbo-abdominal approach, in most cases preceding the adrenalectomy by an exploratory laparotomy. The descriptions and weights of the adrenals do not in all cases bear out the statement that they were enlarged. The authors place great importance upon the fuchsinophile reaction of Vines which they claim is a definite evidence of abnormal function. The chapter on the psychologic aspects of the syndrome is interesting but not fully convincing.

In the chapter on biochemistry, a considerable amount of work on the bio-assay of androgens has been performed which would make it appear that in these cases definite increase of androgens is noted. Probably the most important contribution is that of Marrian and Butler who have isolated a new steroid from the urine of bearers of adrenal tumors.

In spite of its shortcomings, this book must be considered a pioneer attempt at investigation of the adrenal cortical syndrome. No one interested in this subject should fail to read it.

—R. T. Frank.

The present widespread interest in the subject of genitoinfectious diseases makes the appearance of this book, *Syphilis, Gonorrhea and the Public Health*¹⁸ by Nelson and Crain, a very timely one. The official positions and the experience of the authors have enabled them to handle the subject in an authoritative and favorable manner. There can be little doubt that the sudden activity in recent months for the control of the diseases discussed has left not only public health workers but physicians and other interested parties far behind in the knowledge of the present status of the treatment and public health aspects of these diseases. The approach to this problem is most excellently set forth in broad general terms in the chapter on Social Hygiene vs. Public Health.

There is a discussion of these two genitoinfectious diseases from a standpoint of diagnosis, treatment, and communicability as well as an excellent chapter on the granulomas. Of particular interest is the section on communicability of syphilis and gonorrhea. The authors state in the section on statistics that there is an evident decline in mortality from various types of syphilis in certain regional areas, but feel that many certificates of death from syphilis have been incorrectly certified.

The fourth part of the book discusses the control of syphilis and gonorrhea, and includes an evaluation of the laws and regulations as at present constituted. The survey of treatment facilities and the necessity for widespread education of the laity, physician, health officers and allied agencies point to the need for complete frankness in regard to the general attitude of the public toward the two diseases. Later on the methods they propose for administration are presented. The method of combining local and state efforts with Federal Public Health Agencies and support is discussed. The authors outline the need for continuance of prophylactic endeavors through social hygiene programs.

The striking results achieved in the Scandinavian countries in the handling of these problems are presented. Suggestions as to how we may utilize their plans in

¹⁸*Syphilis, Gonorrhea and the Public Health*. By Nels A. Nelson, Director, Division Genitoinfectious Diseases, Massachusetts Department of Public Health, and Gladys L. Crain, R. N., Epidemiologist, Division of Genitoinfectious Diseases, Massachusetts Department of Public Health. The Macmillan Company, New York, 1938.

our enormously greater problem are also discussed. This book should be widely read by physicians and public health workers, nurses, and social hygienists, for there is little that is controversial and much which is authoritative and stimulating in the material presented.

—Philip F. Williams.

This book, *Death Rides With Venus*,¹⁹ is prepared by the Director of the Social Hygiene Foundation of Cleveland, and presents a discussion of venereal diseases in a floridly popular style. Undoubtedly the author's position has made him thoroughly familiar with the bald aspects of the social disease problems as they exist today. With the utmost frankness he discusses the various phases of the problem as they have come to him. The ravages of gonorrhea he discusses in a chapter entitled, "Malignant Coffee Beans"; while the horrors of prostitution are brought out in a chapter entitled, "All Whores Are Lousy." The relationship of the American citizen to this problem of social disease is taken up in the final chapter. A reading of this final chapter should dissipate any smugness or disinterest in a problem which affects labor, business, and the tax bill.

—Philip F. Williams.

The Reverend Tyrer's long years as a marriage counsellor have resulted in the publication of his teachings in this book, *Sex Satisfaction and Happy Marriage*.²⁰ Here Reverend Tyrer discusses the many questions and problems that have come to him, which relate in the most part to sex education for engaged couples, as well as such problems of married people as abortion, birth control, impotence, and frigidity. All of these topics are presented in a thoroughly understandable manner which should suggest a simple line of explanation by the physician or clergyman when confronted with like problems. In the final chapter the Reverend Tyrer moves from the discussion of love, sex, and marriage to a number of small items most of which come up almost daily in conversations with obstetric and gynecologic patients.

Dr. Robert L. Dickinson in a foreword commends the book as an excellent illustration of the standard medical work adapted to the use of the laity.

—Philip F. Williams.

In *The Single Woman and Her Emotional Problems*,²¹ a splendid presentation of the psychosexual problem of women, Dr. Hutton offers help to both the woman herself and her medical advisor. In this edition of the book she has added a chapter explaining the psychologic terms used in the text, which should be of help to lay readers in comprehending the later discussion. That this book was needed is evidenced by the fact that it has appeared in a second English, a Dutch and a Norwegian edition. The single women, of whom there are many in our present mode of life, have problems peculiar to themselves, developing as a result of both normal and abnormal relationships. This book deals in a sympathetic and sane manner with these emotional friendships and sexual problems. The reading of the book should instill sympathy and understanding in a medical advisor, and provide definite and constructive help for the lay reader of the class for whom it is intended.

This edition receives the same warm commendation that was given to its predecessor.

—Philip F. Williams.

¹⁹*Death Rides with Venus*. By Arthur C. Palm. The Greystone Press, New York, 1937.

²⁰*Sex Satisfaction and Happy Marriage*. By the Reverend Alfred Henry Tyrer, Clergyman of the Protestant Episcopal (Anglican) Church. Foreword by Robert L. Dickinson, M.D., New York. Emerson Books, Inc., New York, 1938.

²¹*The Single Woman and Her Emotional Problems*. By Laura Hutton, Physician, Tavistock Clinic, London. Edition 2; 173 pages. William Wood and Co., Baltimore, 1937.

In this small brochure, *Twenty-Eight Years of Sterilization in California*,²² are presented the findings of a second study covering 10,000 cases of eugenic sterilization of selected persons in California State Institutions.

Since 1909 California has been systematically enforcing a eugenic sterilization law, and the immediate conclusions of the operation of this law are presented here. The book deals with the method of operation and application of the law in various types of mental disorders, epilepsy and feeble-mindedness. The authors do not feel that sterilization of these individuals has tended to increase promiscuity, and they show by a comparison with divorce rate among normal people that the marriage of sterilized individuals has been quite satisfactory.

The day has passed when eugenic sterilization can be regarded as an experiment. The conclusions of this little booklet prove its success.

—Philip F. Williams.

The 1936 and 1937 series of lectures to the laity established by the New York Academy of Medicine are presented in *Milestones in Medicine*.²³ Seven lectures deal with such varied topics as psychiatry, heredity, leprosy, and glands of internal secretion. These lectures are not at all in a popular style, but are unique in that they are presented as an historical description of the development of the established facts of a particular subject, and the explanation of the sequence of and reasons for evolution of the subject. Dr. Stoddard's lecture on heredity and Dr. Timme's story of the glands of internal secretion are outstanding.

This collection might well be suggested by an obstetrician as a book to be read by his own patients.

—Philip F. Williams.

In these days of dislocated sociologies and recessive finances a book on *The Physician's Business*²⁴ is opportunely published. Dr. Wolf offers a volume which covers the business and practical aspects of medical practice in a clear and simple manner. It is just possible that he might have added one other chapter to this excellent book on the consideration of whether or not a young man should take up medicine as a career.

Beginning with the selection of hospital internship for the recent graduate, he discusses other opportunities than those offered in private practice, and proceeds to the origin, extent, and selection of a specialty. He offers sage advice in the problem of location and speaks words of wisdom on the manner of professional contacts, with practical suggestions to cordial and ethical relationships with colleagues.

Records, both medical and financial, are discussed in detail. There is included a minimum fee schedule of the Industrial Commission of the State of New York as a suggestive basis for fees. Dr. Wolf offers many series of printable directions which may be useful in either general or special practice. The equipment, personnel, and technic of office practice is thoroughly covered. Such intimate matters as income tax, insurance, and other topics, including legal complications and current trends in practice are brought out.

This is an excellent guide to the material aspects of medicine, and it may well be studied by a young physician as he begins his work, or by an older physician who contemplates a change in his location or type of practice.

—Philip F. Williams.

²²*Twenty-Eight Years of Sterilization in California*. By Paul Popenoe, Sc.D., and E. S. Gosney, B.S., LL.B., Pasadena, 1938.

²³*Milestones in Medicine*. Laity lectures of the New York Academy of Medicine. Introduction by James Alexander Miller, M.D. 276 pages. D. Appleton-Century Company, New York, 1938.

²⁴*The Physician's Business*. Practical and Economic Aspects of Medicine. By George D. Wolf, M.D., Attending Oto-Laryngologist, Sydenham Hospital, New York City, etc. Foreword by Harold Rypins, M.D., F.A.C.P. With 57 illustrations, 384 pages. J. B. Lippincott Company, New York, 1938.

*The Diary of a Surgeon*²⁵ is a lusty, picaresque account of medical conditions in the middle of the eighteenth century. Whether it is actually based on fact, it is impossible for the reviewer to judge, but it has all of the vividness of Defoe or Marryat. It shows the intolerable conditions in the London hospitals of the 18th century, particularly the fatality of childbirth and later takes the reader through a bloody naval battle and an island in the Caribbean infected with yellow fever. It is vivid, coarse, picturesque and fascinating.

—R. T. Frank.

Dr. Sutton offers in this volume on *Physical Diagnosis*²⁶ explicit and detailed instructions in regard to taking a history and making a complete physical examination in any healthy or sick individual. The four cardinal features of such an examination are: inspection, palpation, percussion, and auscultation.

The interesting style in which this book is written deserves special emphasis. This becomes particularly evident in the chapters dealing with the heart and the abdomen. The illustrations throughout the book, several in form of colored plates, greatly enhance the understanding of the reader in regard to many important details of physical examinations for the purpose of exact diagnosis.

All in all this volume represents a noteworthy addition to medical literature.

—Harold Scheff.

On appearance of the first edition of *Progressive Relaxation*,²⁷ in 1929, we described the scope and contents of this most noteworthy contribution to medical literature. It presents a systematic analysis of the neuromuscular states and their significance in medical diagnosis and therapy. Physicians, psychologists and physiologists apparently are evidencing intense interest in this novel problem. Thus it became necessary to prepare a thoroughly revised second edition which embodies all recent work, particularly that of physiologists and psychologists, on reflexes, muscular contraction, sleep, emotion, imagination and other functions. The volume discusses not only the underlying physiologic factors of abnormal muscular states but as well elucidates their connections with various diseases, and describes in detail the methods and procedures by which the desired relaxation and rest actually can be obtained. From this viewpoint alone the book should prove of great practical value to every practitioner of medicine.

—Hugo Ehrenfest.

That this small handbook, *Synopsis of Ano-Rectal Diseases*,²⁸ has reached its fifth edition, is ample evidence that it has met a well-defined need and reflects a growing interest in proctology by the general practitioner.

Various chapters discuss symptoms and their significance, examination of the patient, anesthesia, especially local anesthesia, and details of office treatment. Succeeding chapters discuss particular lesions and their management, although the author has wisely omitted the treatment of the major disturbances of the rectum and colon.

The book is profusely illustrated, particularly with reference to the details of treatment and technic of minor operations. This manual should continue to hold its evident place in the literature of this specialty.

—Philip F. Williams.

²⁵*The Diary of a Surgeon* in the Year 1751-1752. By John Knyveton. Edited by Ernest Gray. 322 pages. D. Appleton-Century Co., New York, 1937.

²⁶*Physical Diagnosis*. By Don C. Sutton, Associate Professor of Medicine, Northwestern University School of Medicine, etc. With 298 Text Illustrations and 8 color Plates. 495 pages. The C. V. Mosby Company, St. Louis, 1937.

²⁷*Progressive Relaxation*. By Edmund Jacobson, A.M., Ph.D., M.D., Laboratory for Clinical Physiology, Chicago. 494 pages. The University of Chicago Press, Chicago, 1938.

²⁸*Synopsis of Ano-Rectal Diseases*. By Louis J. Hirschmann, Professor of Proctology, Wayne University, etc. With 174 text illustrations and 6 color plates, 288 pages. The C. V. Mosby Company, St. Louis, 1937.

As the title indicates this volume is written as a *Textbook of Diagnostic Roentgenology*²⁹ chiefly for students.

Illustrations and legends throughout the book are clear. All technical procedures are explicitly set forth in the various chapters, those not frequently employed more briefly. As the outstanding section of this book we consider that dealing with the osseous system. Table of contents and the index are well arranged and for this reason this volume must be regarded not only as a suitable textbook for students but also as a most useful aid for quick reference.

—P. C. Schnoebelen.

This manual on *Approved Laboratory Technic*³⁰ appeared first as a publication of a Committee of the American Society of Clinical Pathologists. In the present edition the technique and methods offered have been approved by a group of 28 collaborators, and include many methods developed, and appraised as of value, during the past seven years. The book covers the field thoroughly, discussing in the first part the general laboratory methods, in the second part the clinical pathology methods, in the third part the bacteriologic, in the fourth part the serologic, and in the fifth and final part the chemical methods. These various methods discussed include all phases of the activities of the general clinical pathologic laboratory as equipment, animals, technique in animal tests, and technique in clinical examinations such as tests of kidney function, stomach contents, exudate and transudates, etc.

An entire chapter deals with the hormonal diagnosis of early pregnancy and the quantitative methods used in the diagnosis of hydatidiform mole and chorio-epithelioma.

This work may be considered an authoritative standard, which should be of value to the obstetrician and gynecologist who is concerned to any extent with the performance of the laboratory examination of his patient.

—Philip F. Williams.

In *Eat and Keep Fit*³¹ the author presents for the lay public a comprehensive discussion of the nature of our food supply. He discusses in simple terms the constituent elements and food values of the various things we eat from the standpoint of why the body needs them and what happens if they are lacking. He gives a common sense presentation of the present status of the vitamins and emphasizes their importance in language easily understood by the laity. There is an excellent chapter on normal diet, and a rational discussion of methods whereby the body weight may be increased or reduced.

In addition, he presents diets illustrating gain and loss values in foods. There are tables which show caloric and constituent values of common foods. The book is well written, the material simply presented, and can be recommended by physicians to those of their patients interested in the subject.

—Philip F. Williams.

Dr. Pottenger has brought out a fifth edition of his book, *Symptoms of Visceral Disease*.³² In recent years clinical interest in this subject has been increased particularly in regard to the visceral nerves as related to angina and vascular disease.

²⁹*Textbook of Diagnostic Roentgenology*. By Lewis J. Friedmann, M.D., Director, Roentgen Ray Department, Bellevue Hospital, etc. With 638 illustrations, 622 pages. D. Appleton-Century Company, Inc., New York, 1937.

³⁰*Approved Laboratory Technic*. By John A. Kolmer, Professor of Medicine, Temple University, etc., and Fred Boerner, Assistant Professor of Bacteriology, School of Medicine and Graduate School of Medicine, University of Pennsylvania, etc. Edition 2, rewritten, revised, and reset, with 12 plates and 320 illustrations in the text, 893 pages. D. Appleton-Century Co., New York, 1938.

³¹*Eat and Keep Fit*. Scientific Secrets of Diet. By Jacob Buckstein, M.D., Consulting Physician in Disease of the Stomach to Central Islip Hospital, etc. 128 pages. Emerson Books, Inc., New York, 1938.

³²*Symptoms of Visceral Disease*. A Study of the Vegetative Nervous System in Its Relationship to Clinical Medicine. By Francis Marion Pottenger, M.D., Medical Director, Pottenger Sanatorium for Disease of the Chest; Professor of Clinical Medicine, University of Southern California, etc. Edition 5, with 87 text illustrations and 10 color plates, 442 pages. The C. V. Mosby Company, St. Louis, 1938.

In the present edition visceral pain has been made the subject of a separate chapter, and a chapter on vegetative centers of the brain and cord has been added.

The first part of the book deals with a general consideration of the anatomy of the vegetative nervous system, its physiology, pharmacology, and the various phases and theories of cellular activity.

In the second part of the book are discussed the relationship of the vegetative nervous system and symptoms of the visceral disease, and, further, the clinical studies of the viscerogenic reflexes as related to the various systems and organs. It is to be regretted that the work of Cotte has not been taken into consideration in the discussion of the clinical conditions of the urogenital tract. In discussing the inseparability of visceral neurology and endocrinology, separate studies take up the various glands of internal secretion. The author states that no definite relationship between pituitary secretion and nerve stimulation has been shown. This situation differs from that found in two other important organs of internal secretion, adrenal and thyroid, where the activity of the gland is stimulated by the sympathetics.

—Philip F. Williams.

In this small volume, *Wundversorgung und Wundbehandlung*³³ Dr. von Seemen presents a thorough consideration of surgical incisions. The physiology of the healing of such incisions is followed by a discussion of the technique and care of incisions, a short consideration of drainage in relation to wound healing, and the pathologic processes in infected wounds. He describes the relation of physical and chemical disinfection of the skin in relation to wound healing, and presents several graphs to illustrate the relationship between the general physiology of the body to extensive surgery of the surface.

There is a short chapter on the use of electric knives and needles and the healing of wounds so produced. In a brief appendix he lists the various disinfecting, stimulating, and coagulating materials used in his clinic, and a list of the sera used for tetanus, gas edema, and other anaerobic complications.

—Philip F. Williams.

Item

American Board of Obstetrics and Gynecology, Inc.

The next examinations (written and review of case histories) for Group B candidates will be held in various cities of the United States and Canada on Saturday, November 5, 1938, at 2:00 P.M., and on Saturday, February 4, 1939. Application for admission to the written examination scheduled for February 4, 1939, must be filed on an official application form in the office of the Secretary at least sixty days prior to this date (or before December 4, 1938).

The general oral, clinical and pathological examinations for all candidates (Groups A and B) will be conducted by the entire Board, meeting in St. Louis, Missouri, on May 15 and 16, 1939, immediately prior to the annual meeting of the American Medical Association. Application for admission to Group A examinations must be on file in the Secretary's Office before April 1, 1939.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Bldg., Pittsburgh (6), Pa.

The following names were not included in the previous list of candidates certified by the American Board of Obstetrics and Gynecology but received certification at the San Francisco meeting in June, 1938:

GEORGE E. KLEEMAN, JR., Oakland, Calif.

MAURICE L. HORWITZ, Oakland, Calif.

GEORGE W. HEWITT, Los Angeles, Calif.

³³*Wundversorgung und Wundbehandlung*. By Professor Dr. H. v. Seemen. Chirurgische Universitäts-Klinik München. 66 pages. Ferdinand Enke, Stuttgart, 1938.